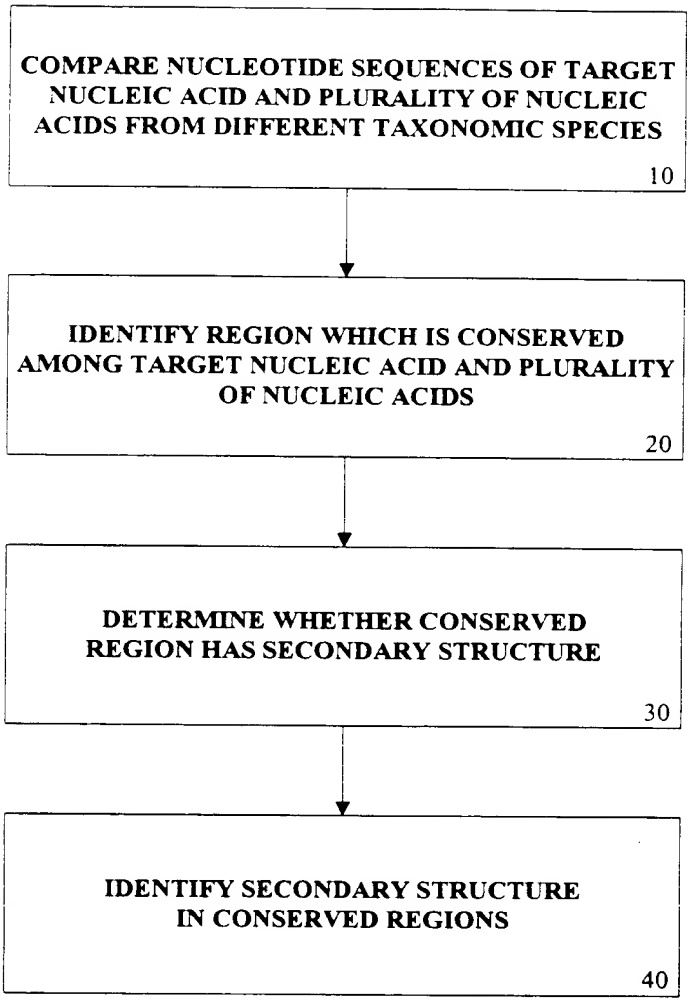

COMPARE NUCLEOTIDE SEQUENCES OF TARGET NUCLEIC ACID AND PLURALITY OF NUCLEIC ACIDS FROM DIFFERENT TAXONOMIC SPECIES
10
IDENTIFY REGION WHICH IS CONSERVED AMONG TARGET NUCLEIC ACID AND PLURALITY OF NUCLEIC ACIDS
20
DETERMINE WHETHER CONSERVED REGION HAS SECONDARY STRUCTURE
30
IDENTIFY SECONDARY STRUCTURE IN CONSERVED REGIONS
40

FIGURE 1

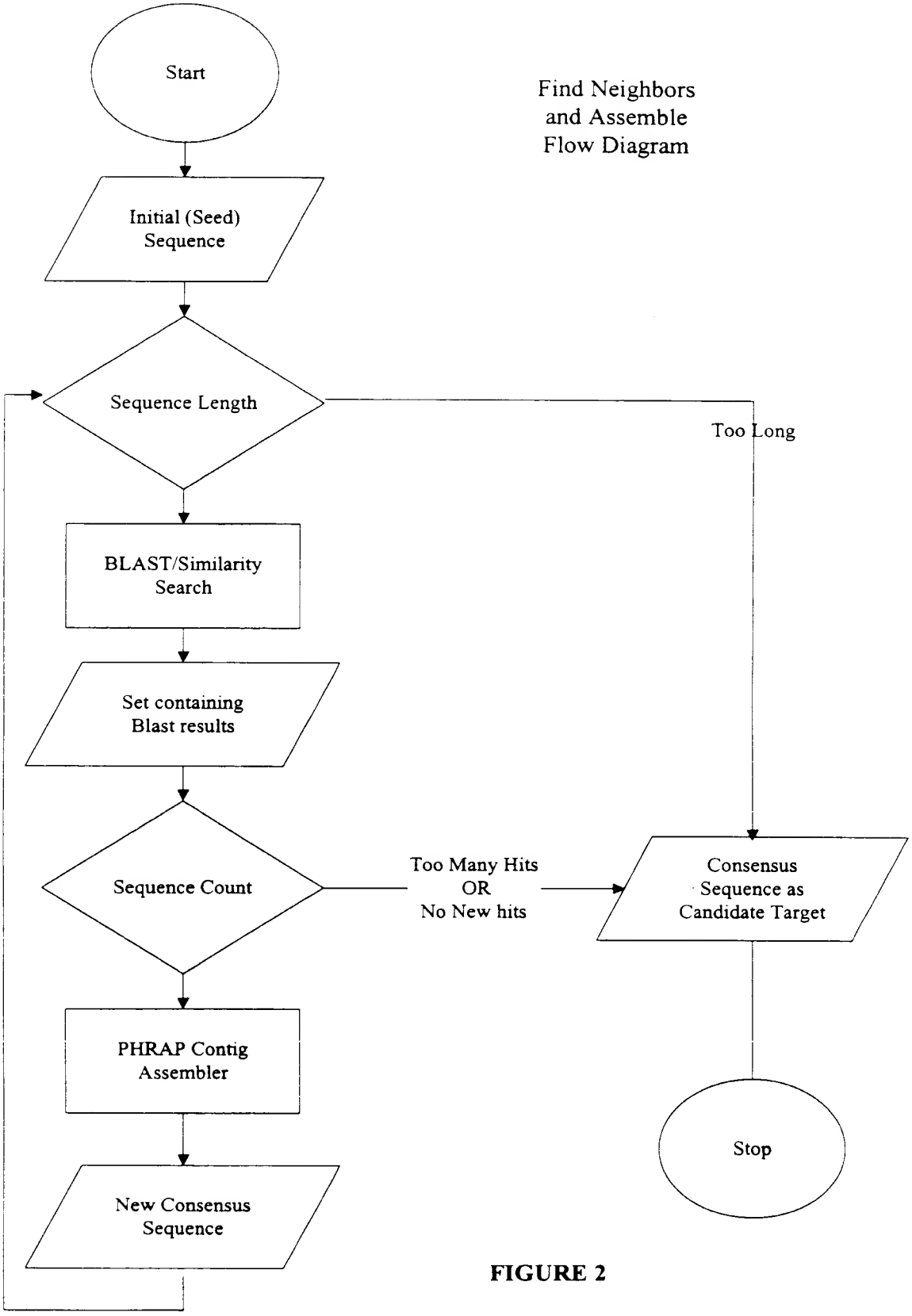

Find Neighbors
and Assemble
Flow Diagram
Start
Initial (Seed)
Sequence
Sequence Length
Too Long
BLAST/Similarity
Search
Set containing
Blast results
Sequence Count
Too Many Hits
OR
No New hits
Consensus
Sequence as
Candidate Target
PHRAP Contig
Assembler
Stop
New Consensus
Sequence

FIGURE 2

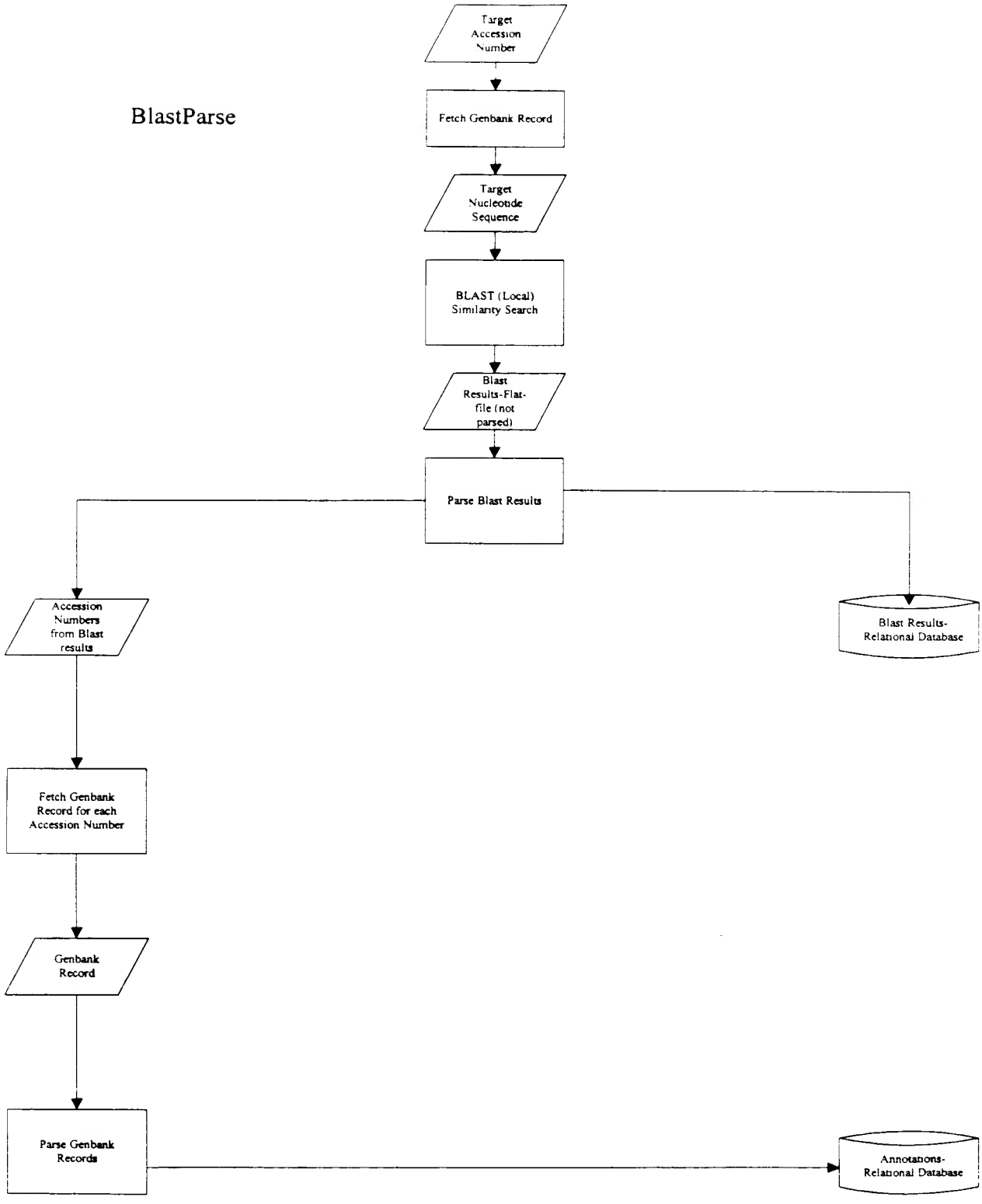

BlastParse
Target Accession Number
Fetch Genbank Record
Target Nucleotide Sequence
BLAST (Local) Similarity Search
Blast Results-Flat-file (not parsed)
Parse Blast Results
Blast Results-Relational Database
Accession Numbers from Blast results
Fetch Genbank Record for each Accession Number
Genbank Record
Parse Genbank Records
Annotations-Relational Database

FIGURE 3

Q-Compare

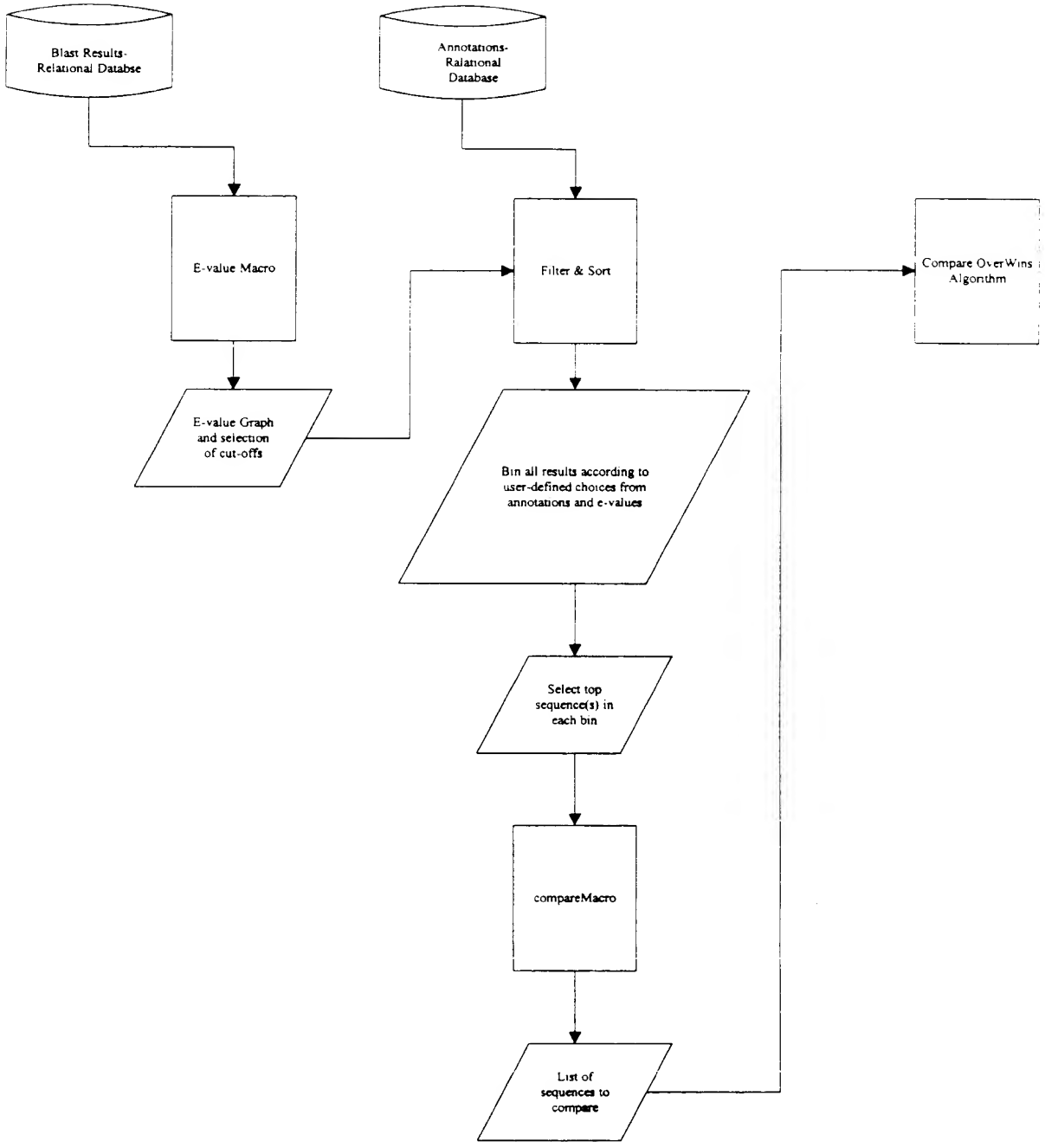


FIGURE 4

CompareOverWins Algorithm Flow Chart

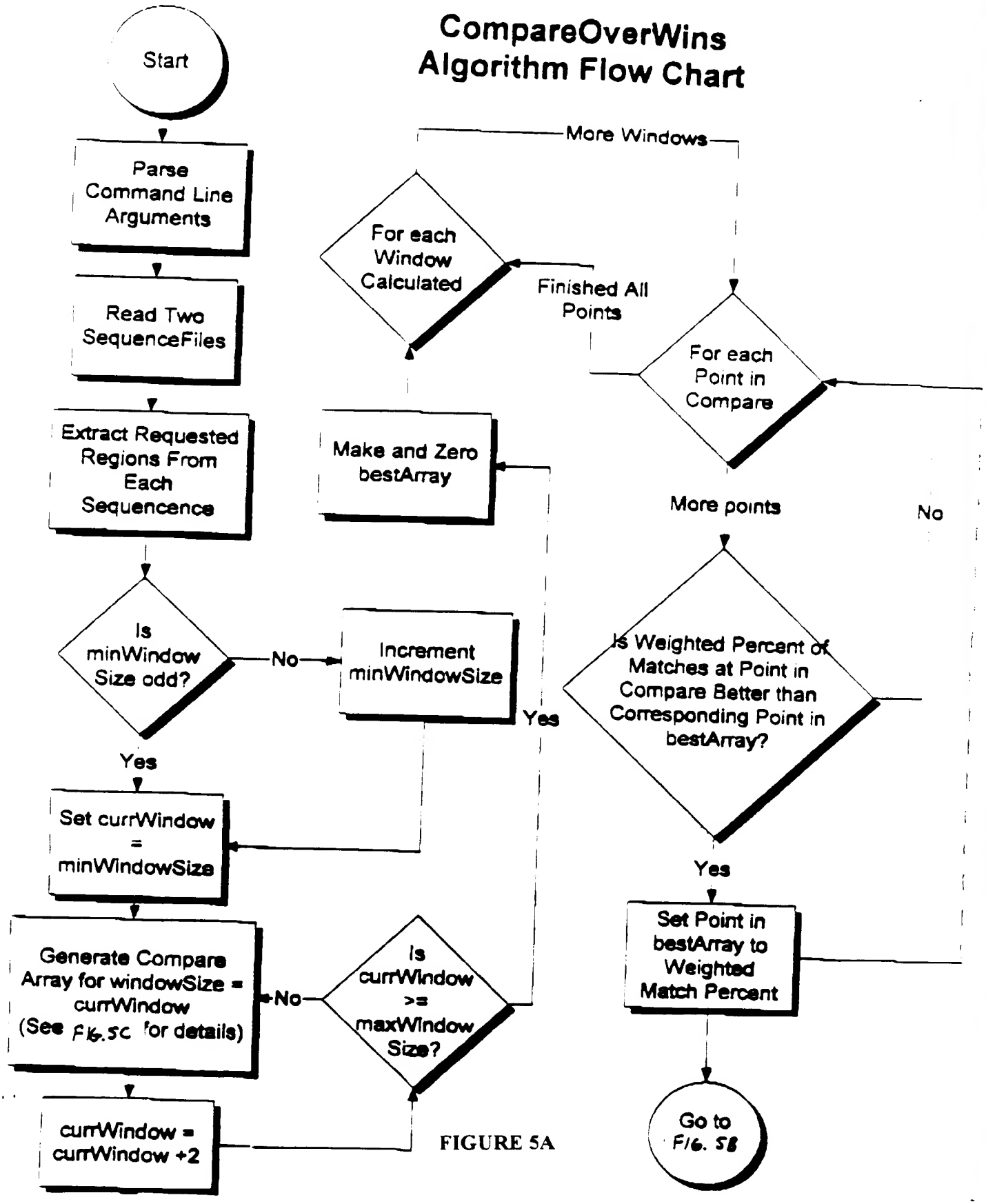


FIGURE 5A

CompareOverWins Algorithm Flow Chart

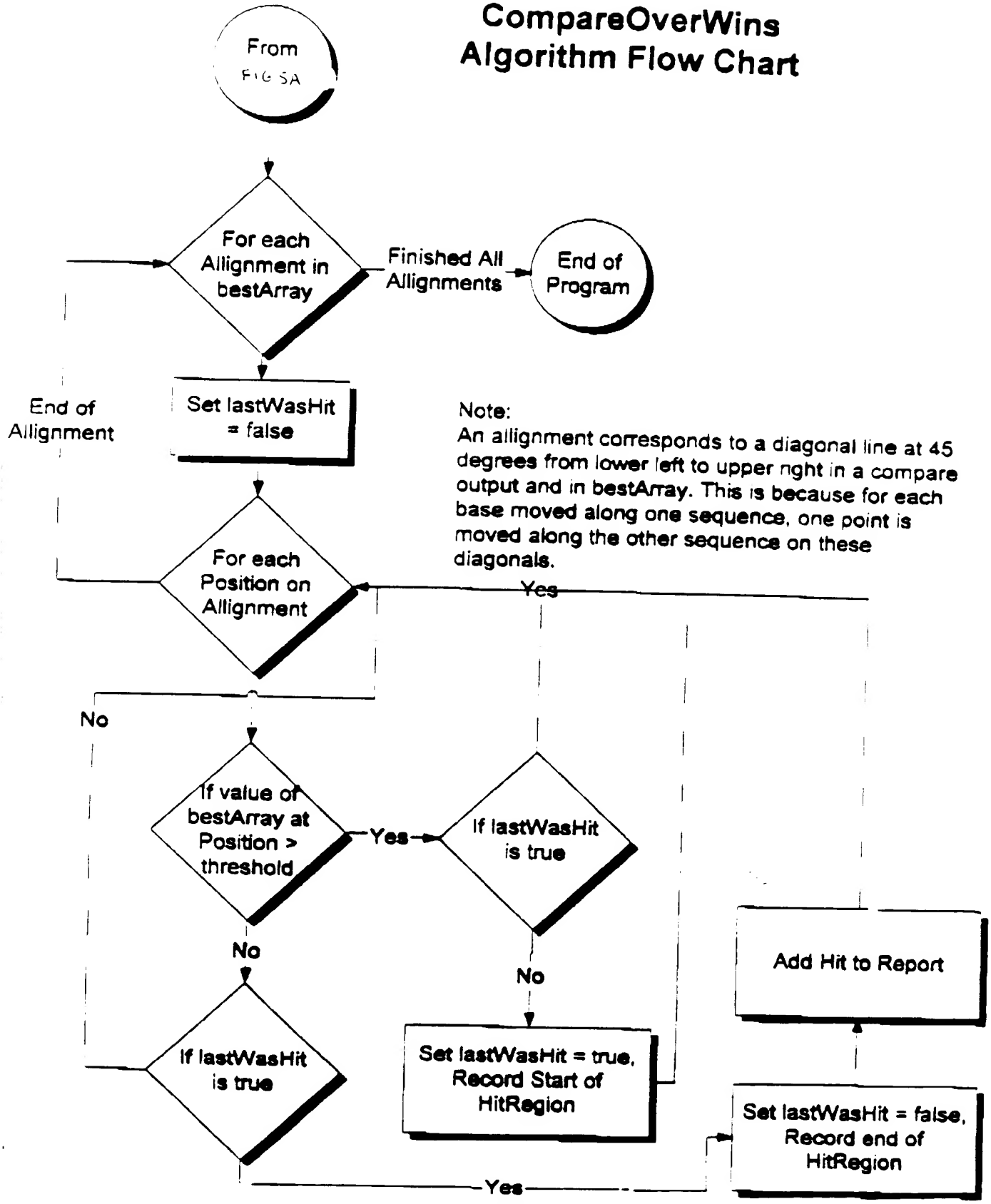


FIGURE 5B

CompareOverWins Algorithm Flow Chart Basic Compare

Input:
Sequence A length a
Sequence B length b
Window Size

Output:
Array of size a by b of unsigned chars (0-255)
Each point represents the number of matches in the window at that allignment and position

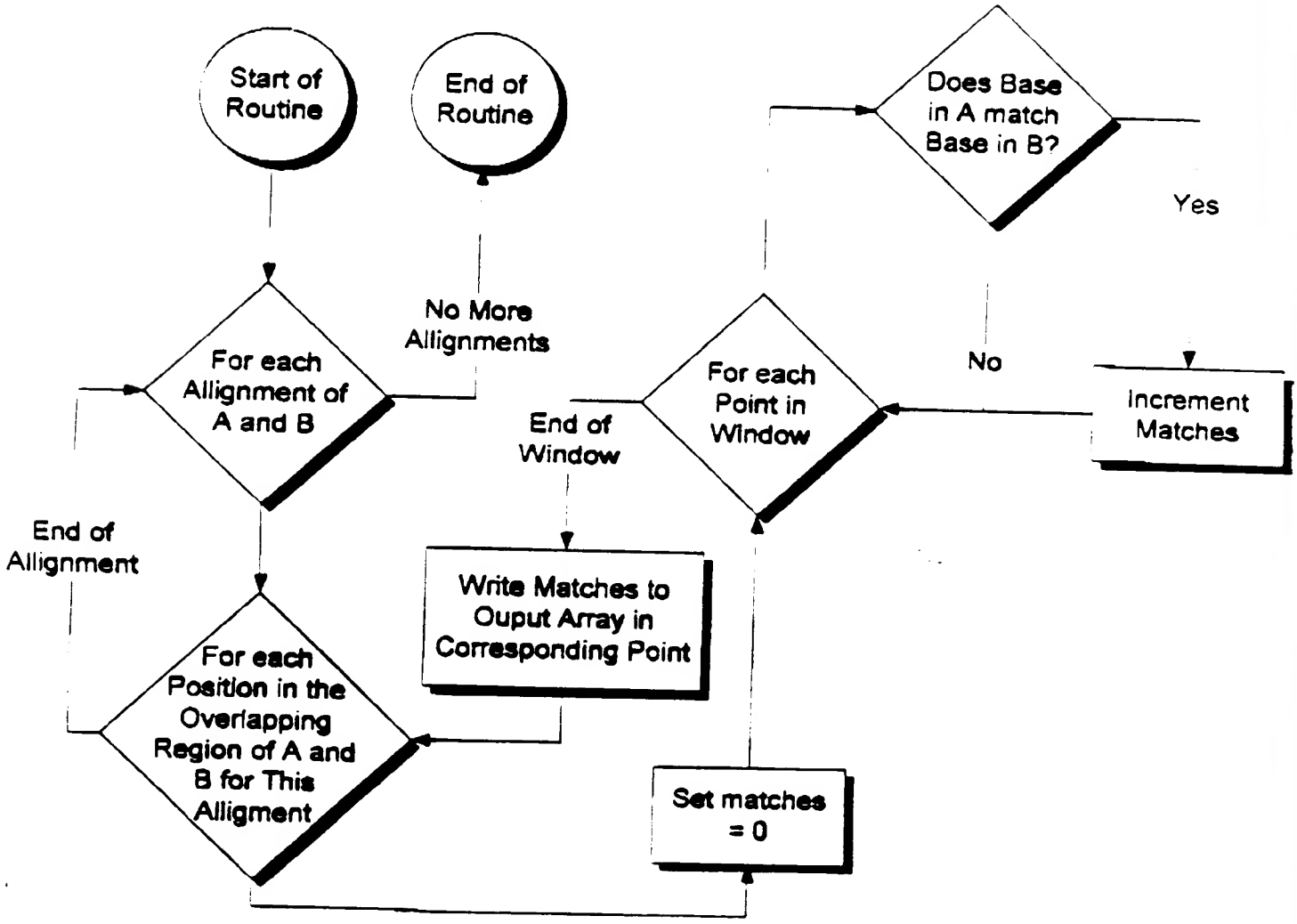


FIGURE 5C

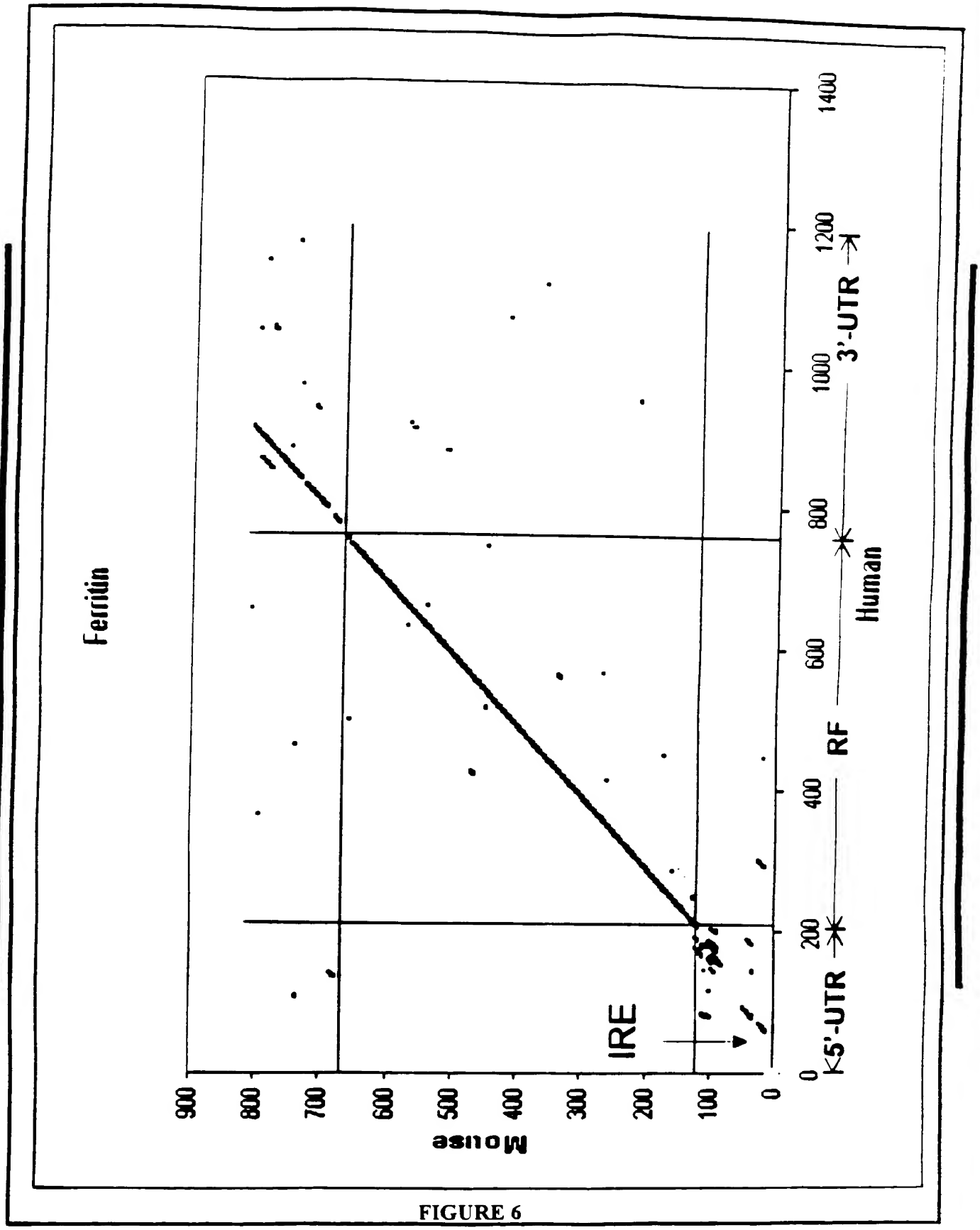

Ferritin
Mouse
900
800
700
600
500
400
300
200
100
0
IRE
0
200
400
600
800
1000
1200
1400
5'-UTR
RF
Human
3'-UTR

FIGURE 6

Self Complementation Analysis - Single Sequence

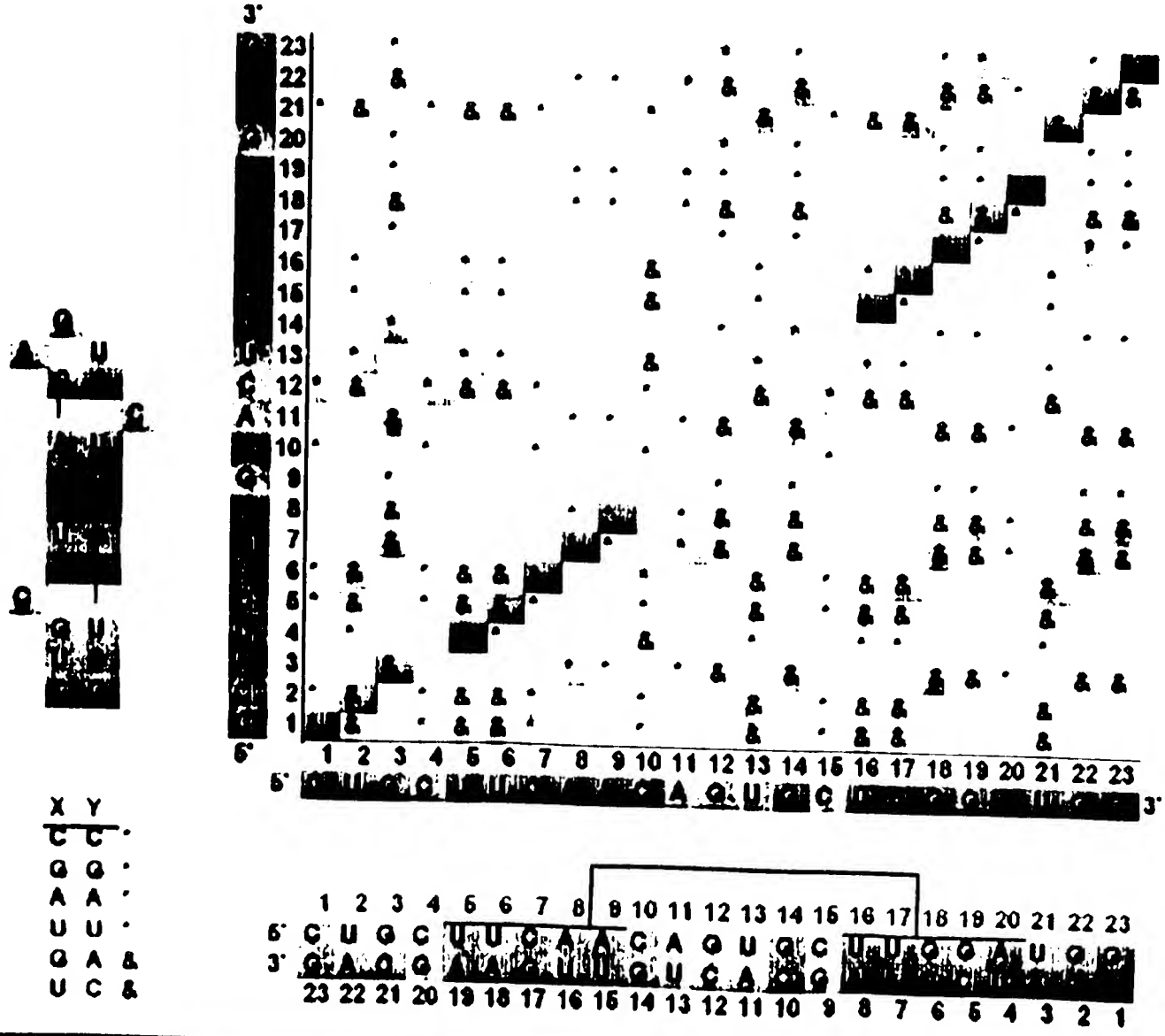


FIGURE 7

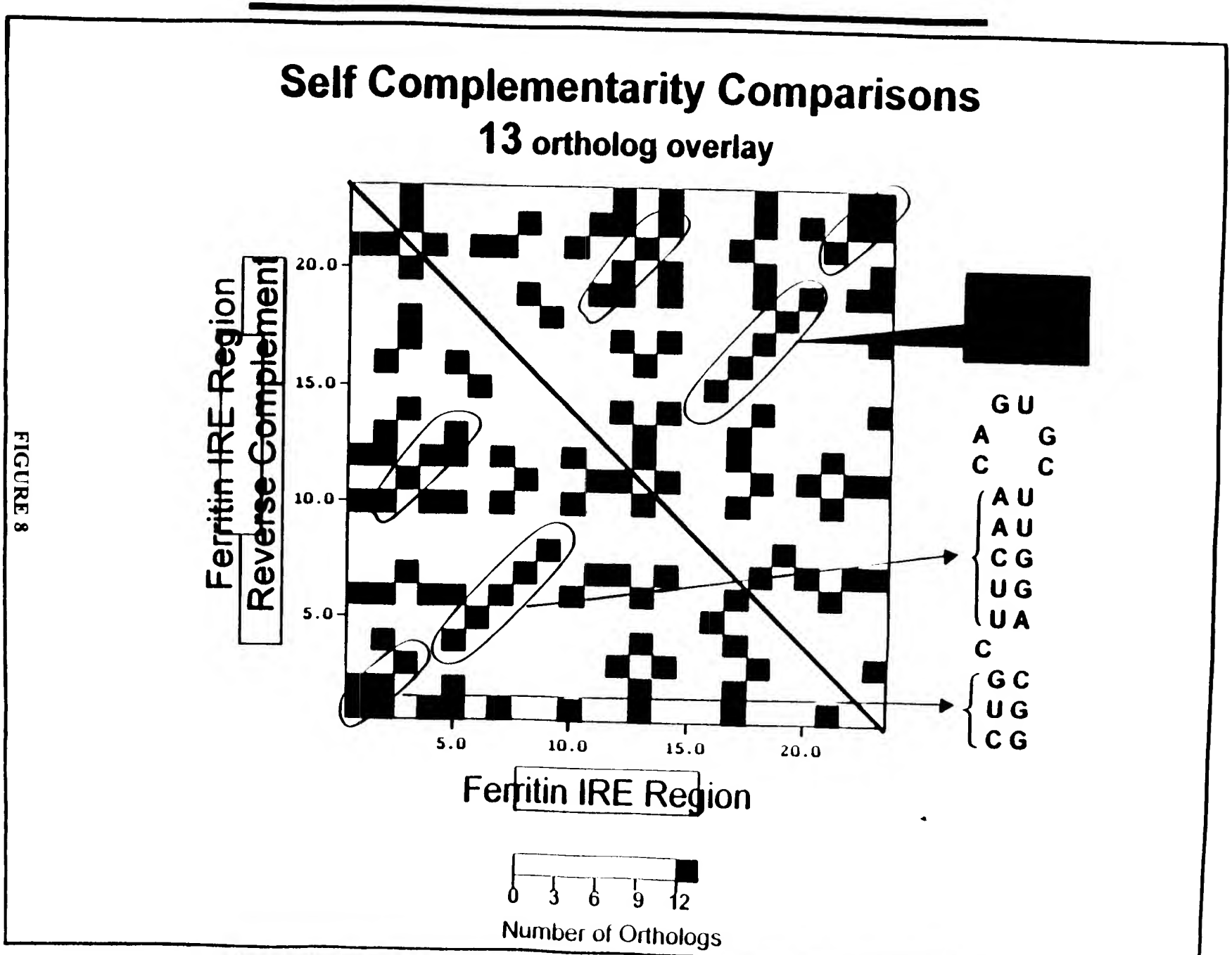
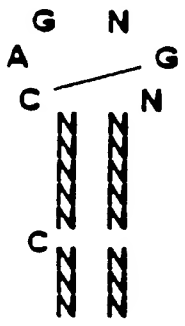

Self Complementarity Comparisons
13 ortholog overlay
Ferritin IRE Region
Reverse Complement
20.0
15.0
10.0
5.0
5.0
10.0
15.0
20.0
Ferritin IRE Region
G U
A G
C C
A U
A U
C G
U G
U A
C
G C
U G
C G
0 3 6 9 12
Number of Orthologs

FIGURE 8

Typical Descriptor

This is an example of a descriptor used to identify iron response elements. To search the database using RNAMOT, the stem-loop model is converted to a text string as shown below:



IRE

Stem-loop Model

H1 S1 H2 S2 H2 H1

H1 3:3 NNN:NNN
S1 1 C
H2 5:5 NNNNN:NNNNN
S2 6 CAGNGN

W2
M0

IRE String descriptor

This descriptor allows for a wobble (W) of 2 (allows G-U pairing) and no mismatches. N can be any nucleotide
H refers to the stem region while S refers to the single stranded region.

FIGURE 9

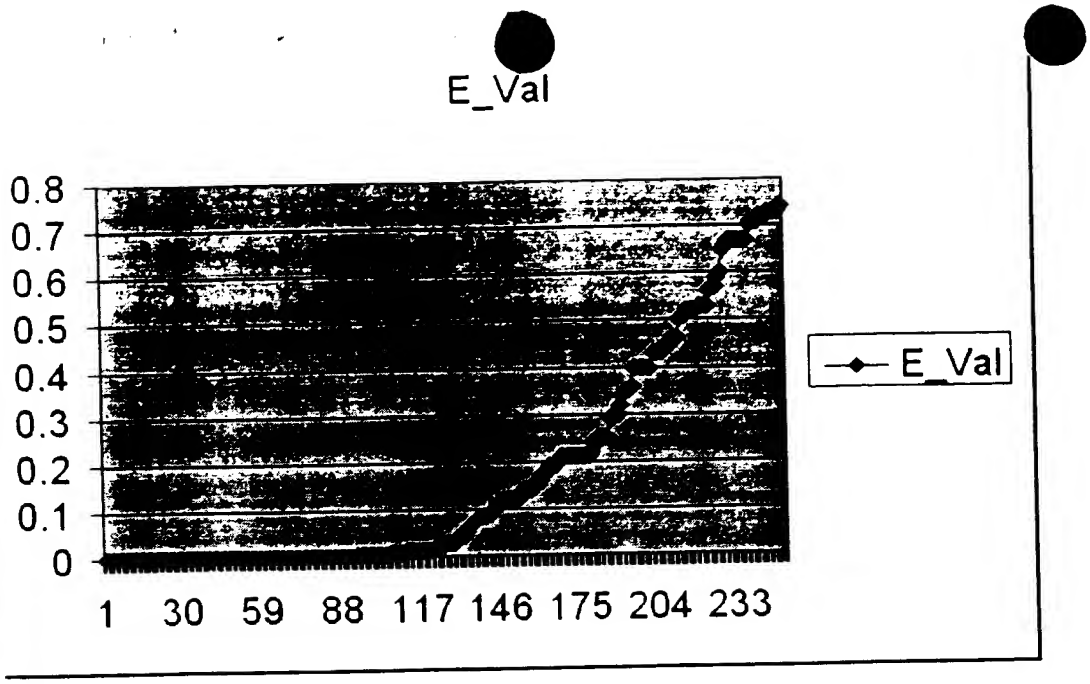


FIGURE 10

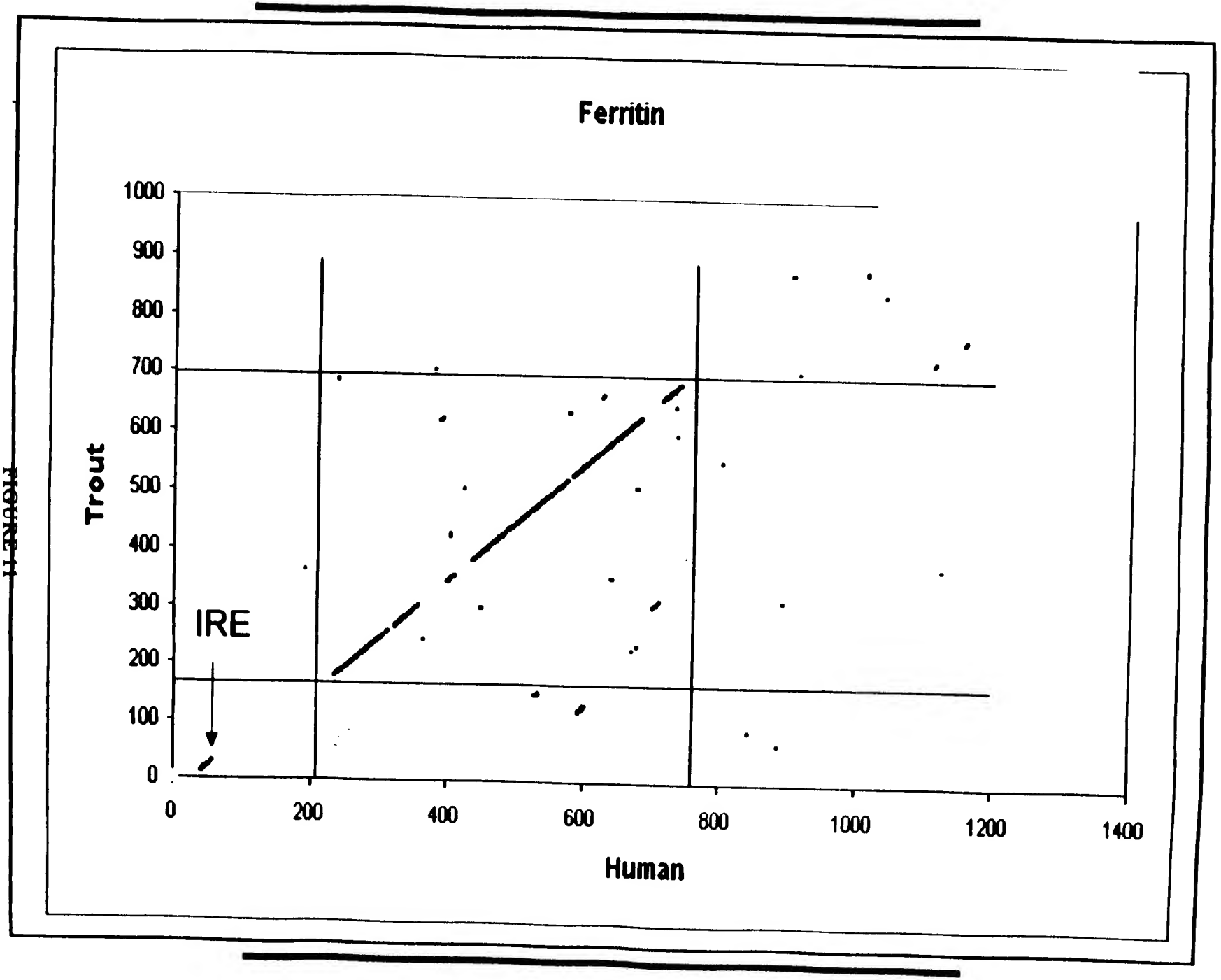

Ferritin
Trout
Human
IRE
0
100
200
300
400
500
600
700
800
900
1000
0
200
400
600
800
1000
1200
1400

FIGURE 11

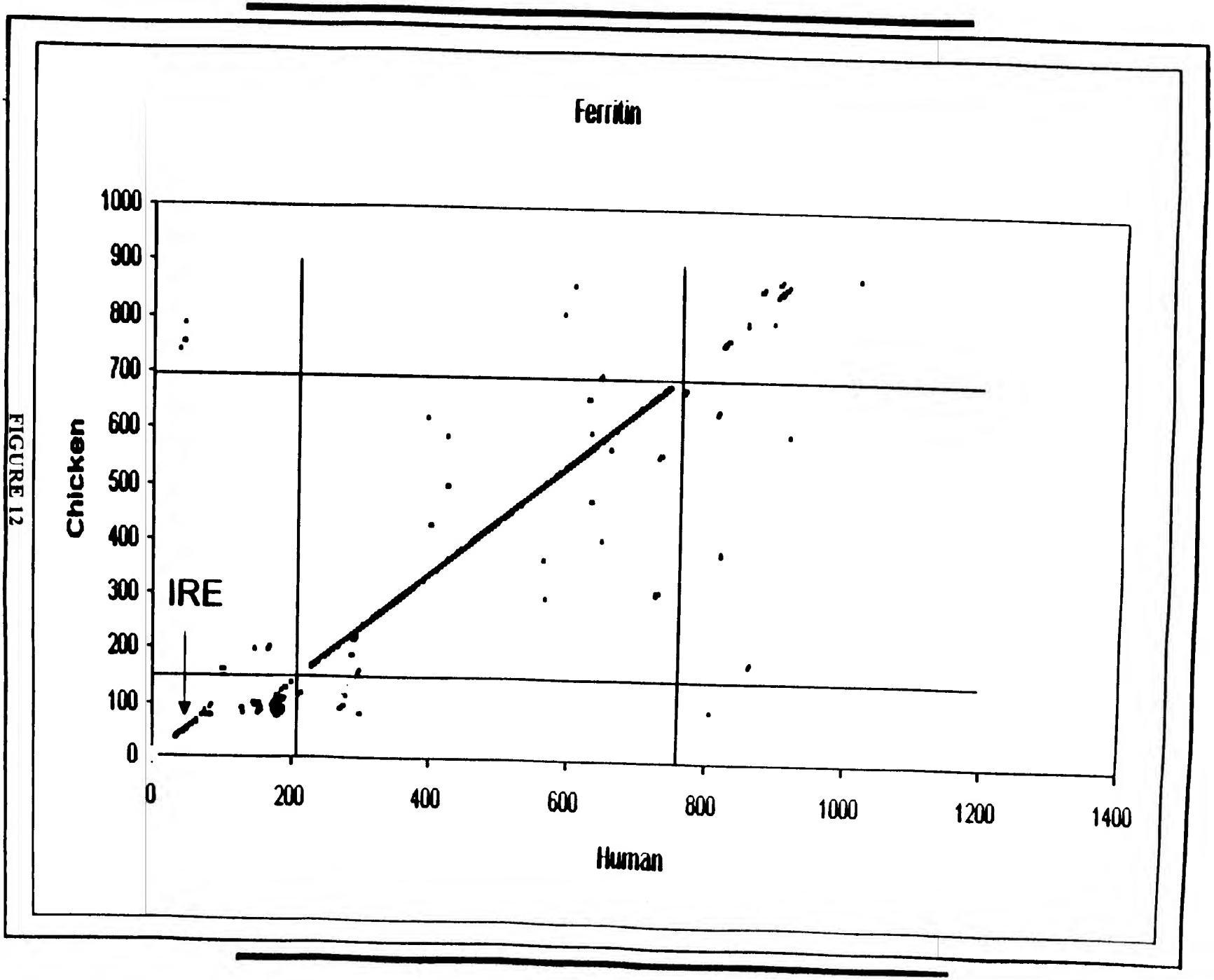

Ferritin
Chicken
Human
IRE
0
100
200
300
400
500
600
700
800
900
1000
0
200
400
600
800
1000
1200
1400

FIGURE 12

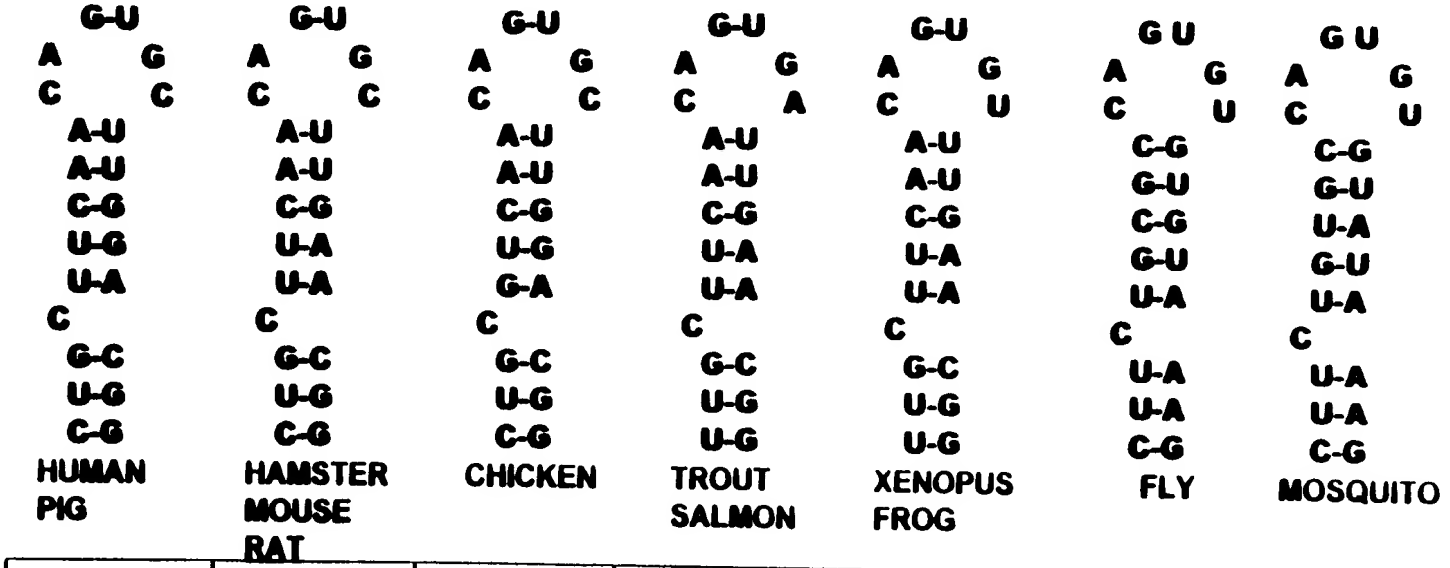
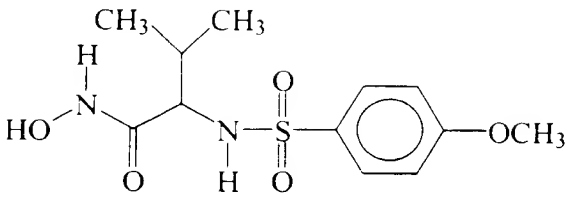


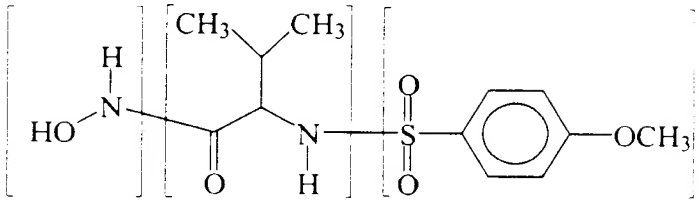
FIGURE 13

HUMAN PIG	No	No	Yes	Yes	Yes	No	No
HAMSTER MOUSE RAT		No	Yes	Yes	Yes	No	No
CHICKEN			No	Yes	Yes	No	No
TROUT SALMON				No	Yes	Yes	Yes
XENOPUS FROG					No	Yes	Yes
FLY						No	Yes
MOSQUITO							No

Compound CI



$C_{12}H_{18}N_2O_5S$



	F_i	F_{ii}	F_{iii}
Molecular formula	H_2NO	C_5H_9NO	$C_7H_7O_3S$

FIGURE 14

Addition of fragments to yield compounds

Table

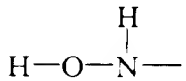
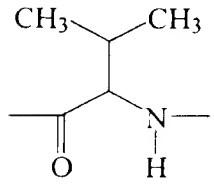
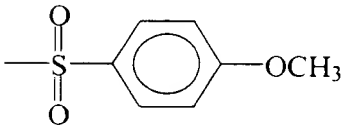
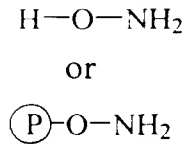
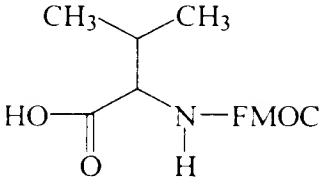
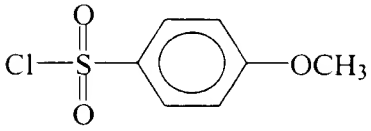
Fragment Identifier	Structure	Name	Molecular formula	Other
F_i		Hydroxylamine	H_2NO	...
F_{ii}		Amino acid	C_5H_9NO	...
F_{iii}		Sulfonyl	$C_7H_7O_3S$	...

FIGURE 15

Reagents	Identifier	Name	Properties
	R_i	Hydroxylamine	...
	R_{ii}	FMOC blocked amino acid	...
	R_{iii}	Sulfonylchloride	...

Ⓟ = Solid support

FIGURE 16

Transformation

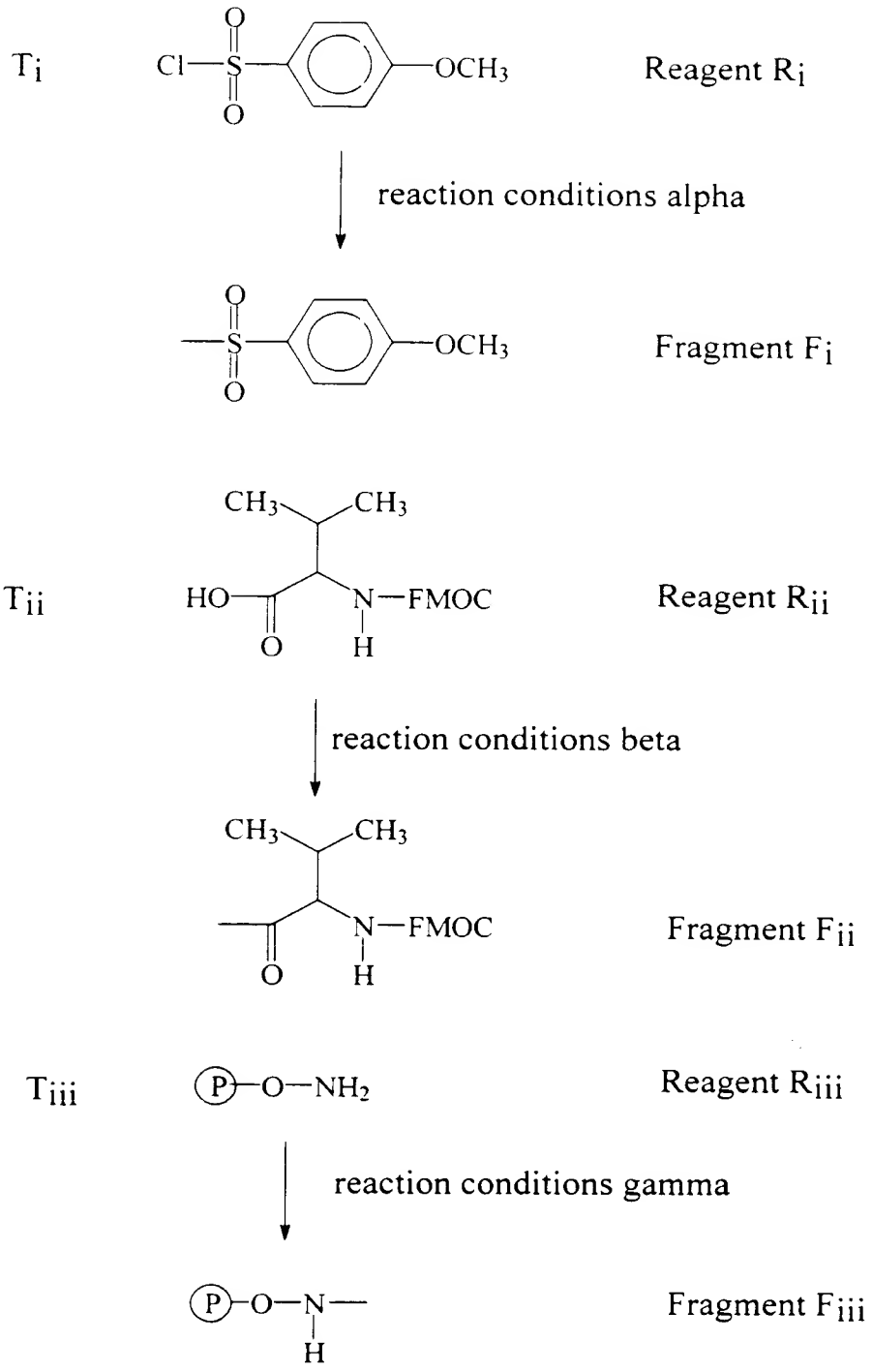


FIGURE 17

Common Fragment / Different Reagents and Transformations

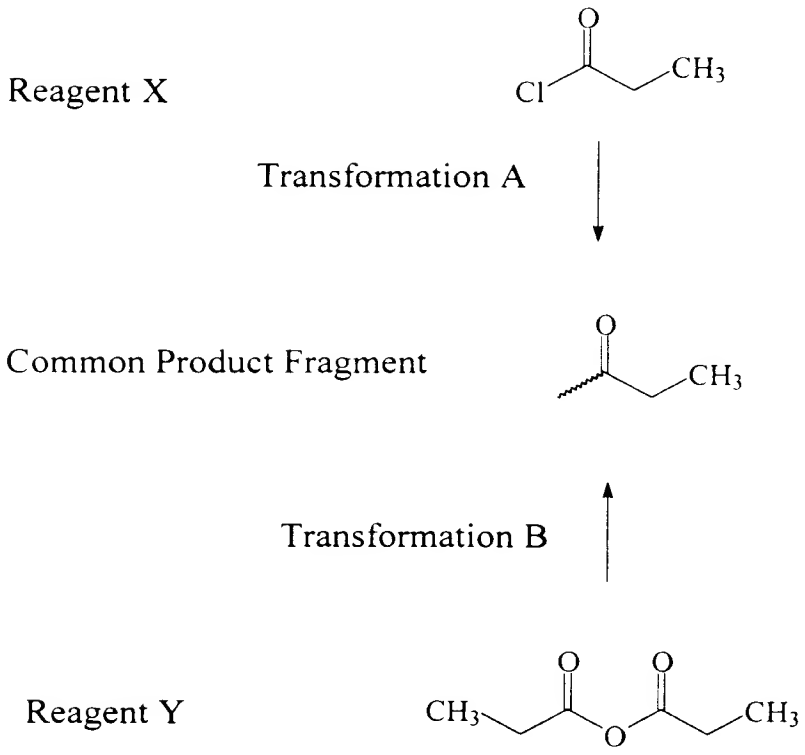


FIGURE 18

Common Fragment / Different Reagents and Transformations

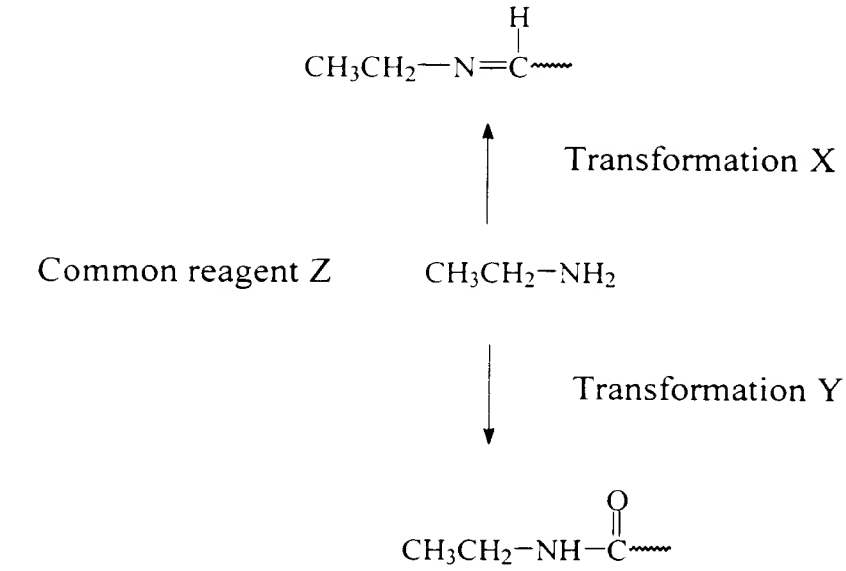


FIGURE 19A

Common Reagent

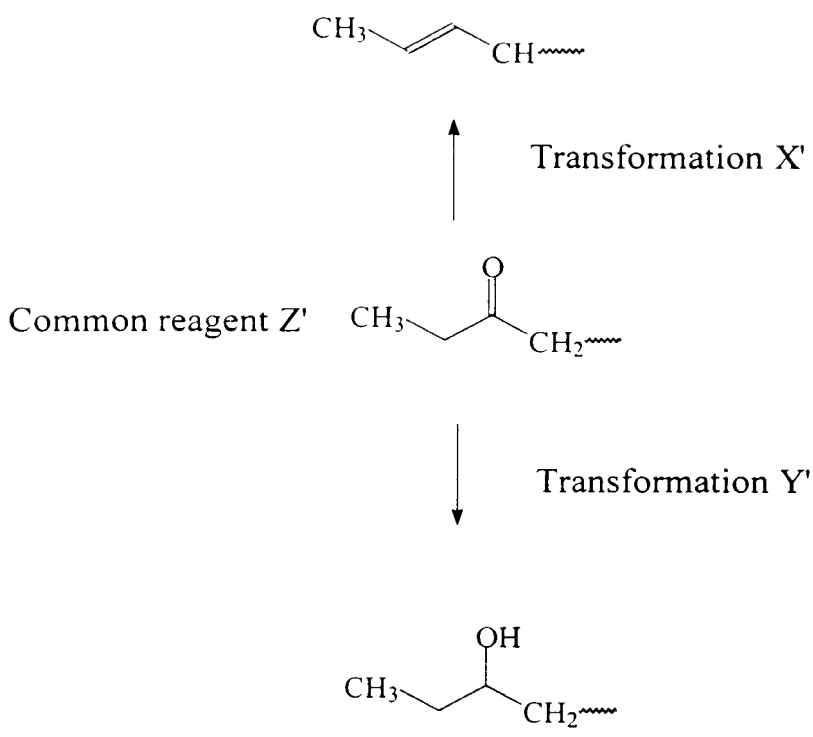
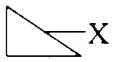
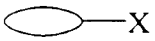
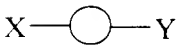
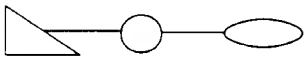


FIGURE 19B

Symbolic addition of fragments to yield compound

Symbolic Structure	Symbolic Identifier	Molecular formula
Fragment		
	$F_{i'}$	$C_uH_vN_w$ ...
	$F_{ii'}$	$C_uH_vN_w$ ...
	$F_{iii'}$	$C_uH_vN_w$ ...
Compound		
	CI'	$C_uH_vN_w$ ...

$$\begin{array}{l} \text{Molecular formula } F_{i'} \\ + \\ \text{Molecular formula } F_{ii'} \\ + \\ \underline{\text{Molecular formula } F_{iii'}} \\ = \text{Molecular formula } CI' \end{array}$$

FIGURE 20

Symbolic Reagent Table

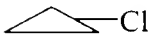
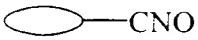
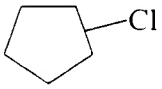
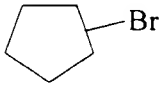
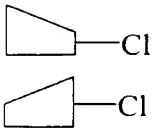
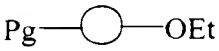
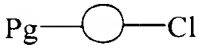
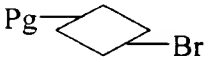
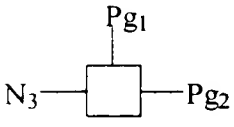
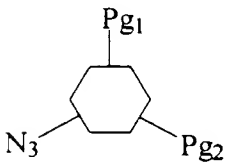
Identifier	Name	Structure	Molecular formula
R1	xxx		xxx
R2	...		...
R3	...		...
R4	...		...
R5	...		...
R6	...		...
R7	...		...
R8	...		...
R9	...		...
R10	...		...

FIGURE 21

Symbolic Fragment Table

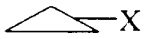
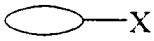
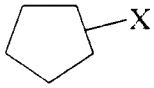
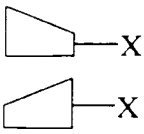
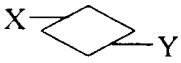
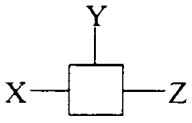
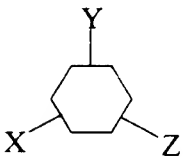
Identifier	Symbolic Structure	Molecular formula	Molecular Weight
F1		xxx	xxx
F2		...	...
F3		...	...
F4		...	...
F5		...	...
F6		...	...
F7		...	...
F8		...	...

FIGURE 22

Symbolic Transformation Table

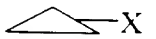
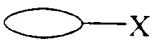
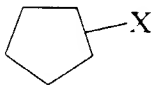
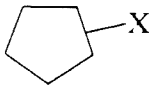
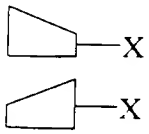
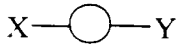
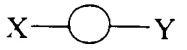
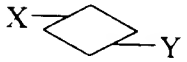
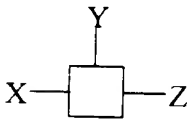
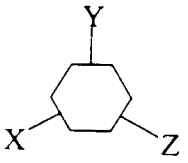
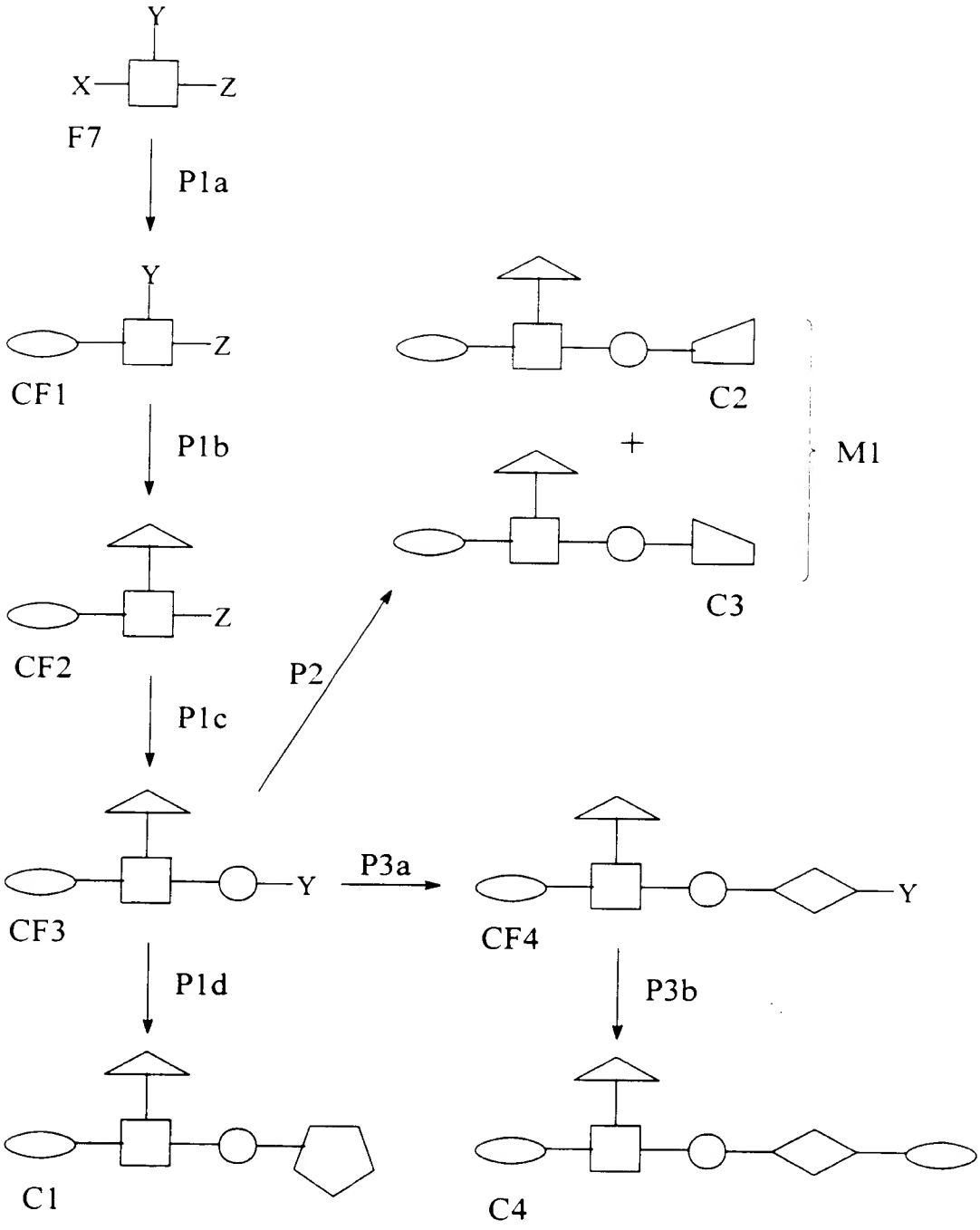
Identifier		Symbolic Reactions	Reagent
T1	F1	 R1	conditions α
T2	F2	 R2	conditions β
T3	F3	 R3	conditions α
T4	F3	 R4	conditions α
T5	F4	 R5	conditions α
T6	F5	 R6	conditions ε
T7	F5	 R7	conditions α
T8	F6	 R8	conditions α
T9	F7	 R9	conditions γ
T10	F8	 R10	conditions γ

FIGURE 23

Single Compounds and Mixtures



P = synthetic path
F = fragment
C = compound

CF = complex fragment
M = mixture

FIGURE 24

Mixture 2

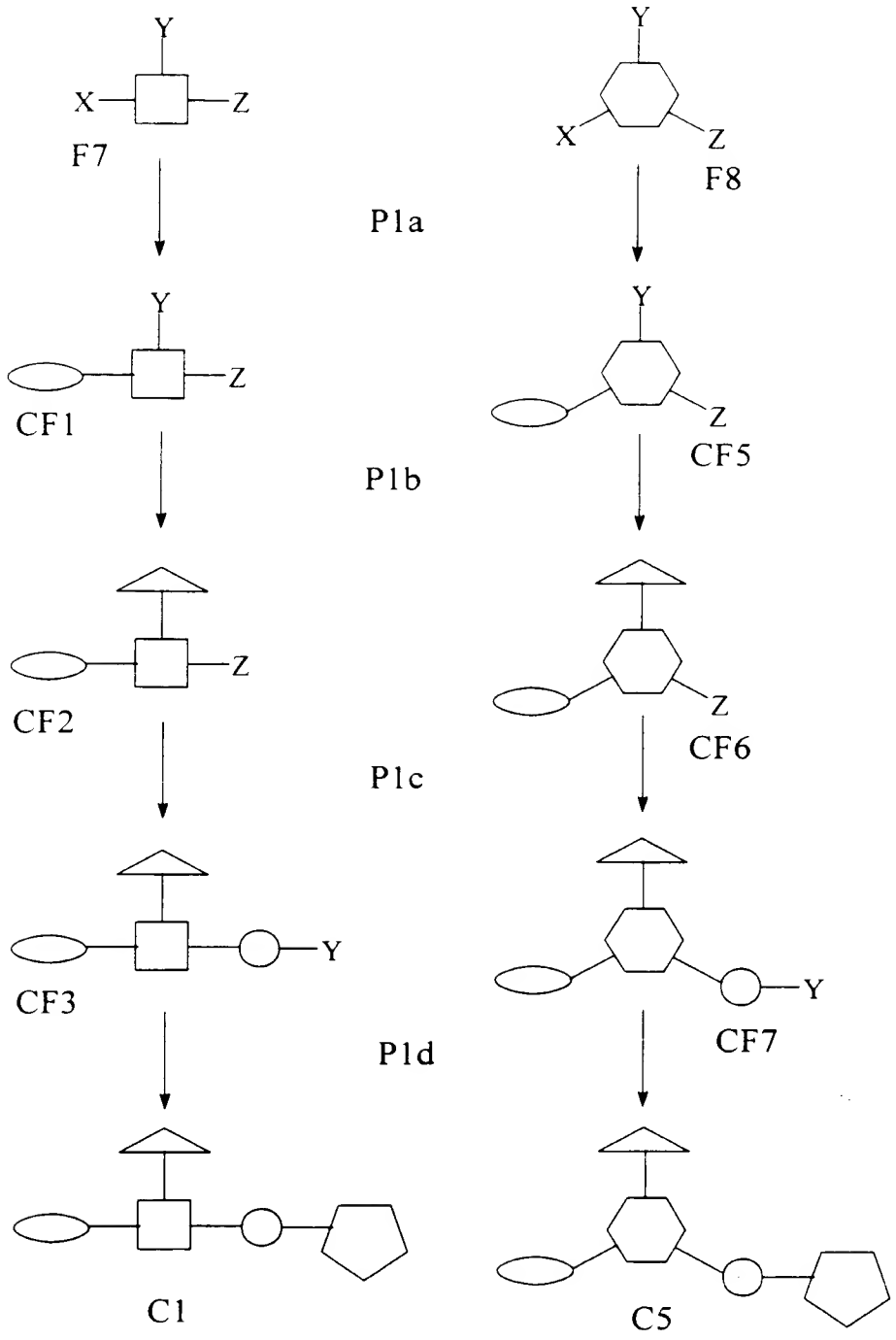


FIGURE 25

Mixture 3

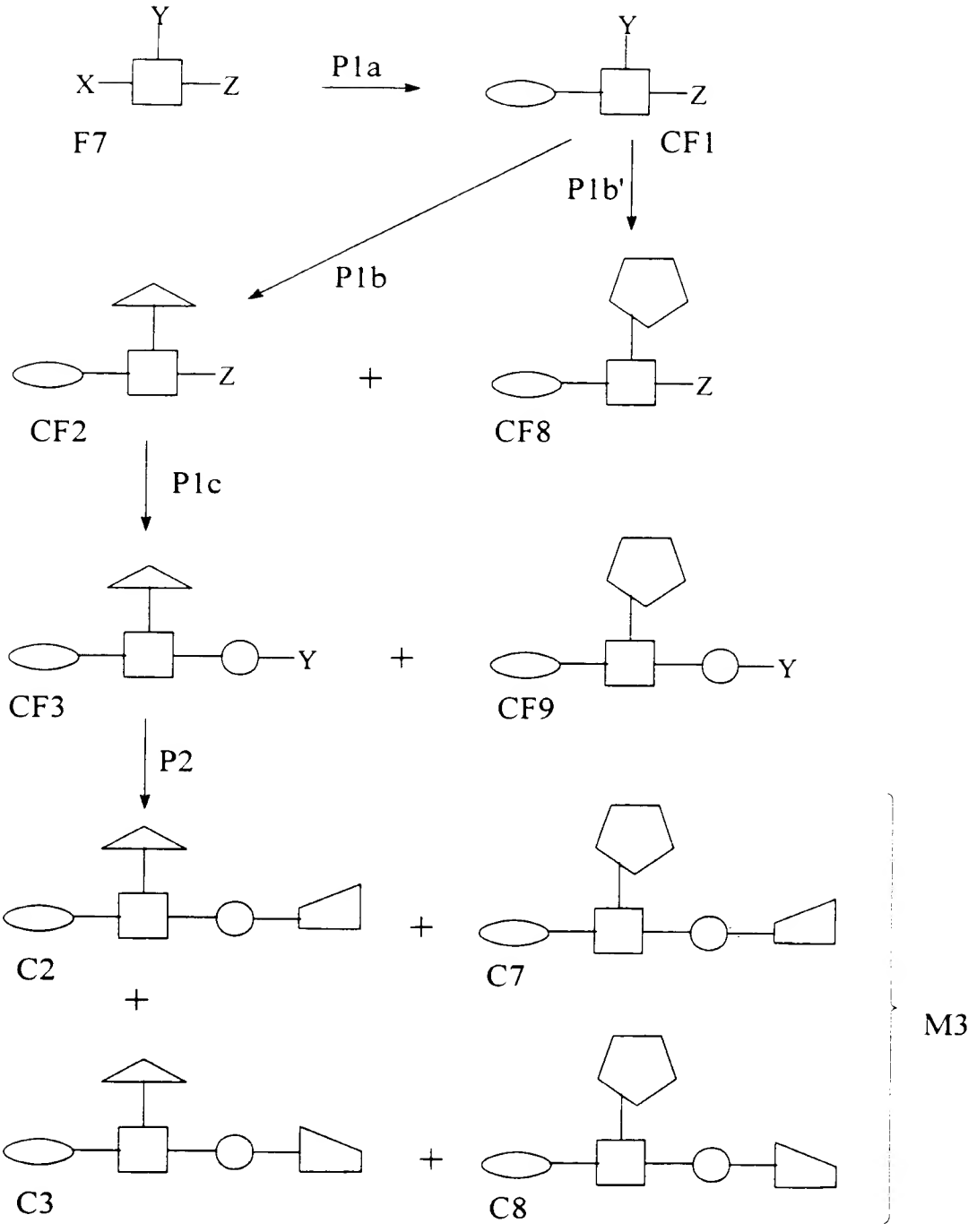
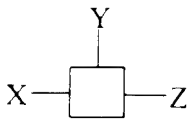


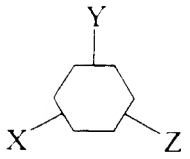
FIGURE 26

Mixture 4

2 Starting Fragments

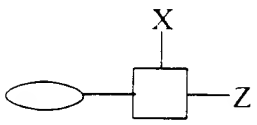


F7

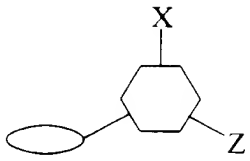


F8

2 Complex Fragments

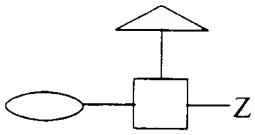


CF1

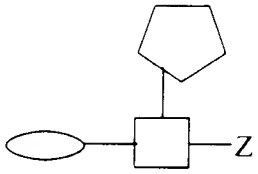


CF5

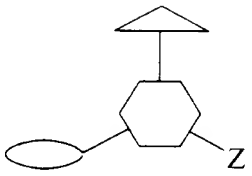
4 Complex Fragments



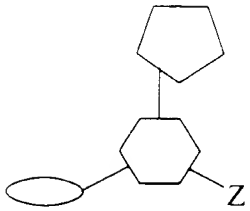
CF2



CF8

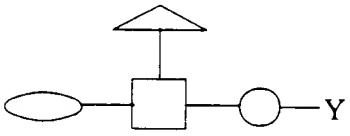


CF 6

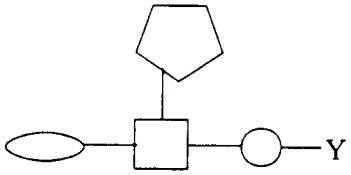


CF11

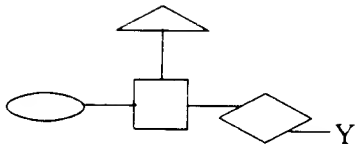
8 Complex Fragments



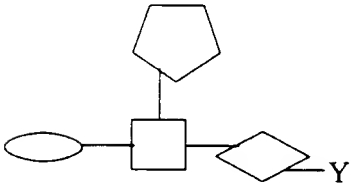
CF3



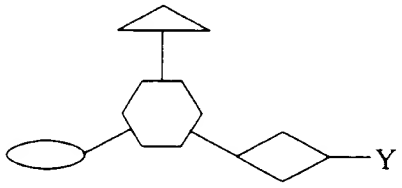
CF9



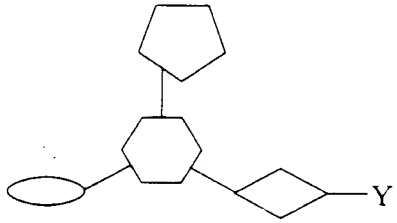
CF12



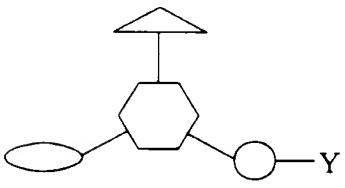
CF13



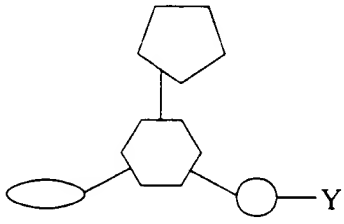
CF15



CF16



CF 7



CF14

FIGURE 27A

Mixture 4 (continued)

16 compounds

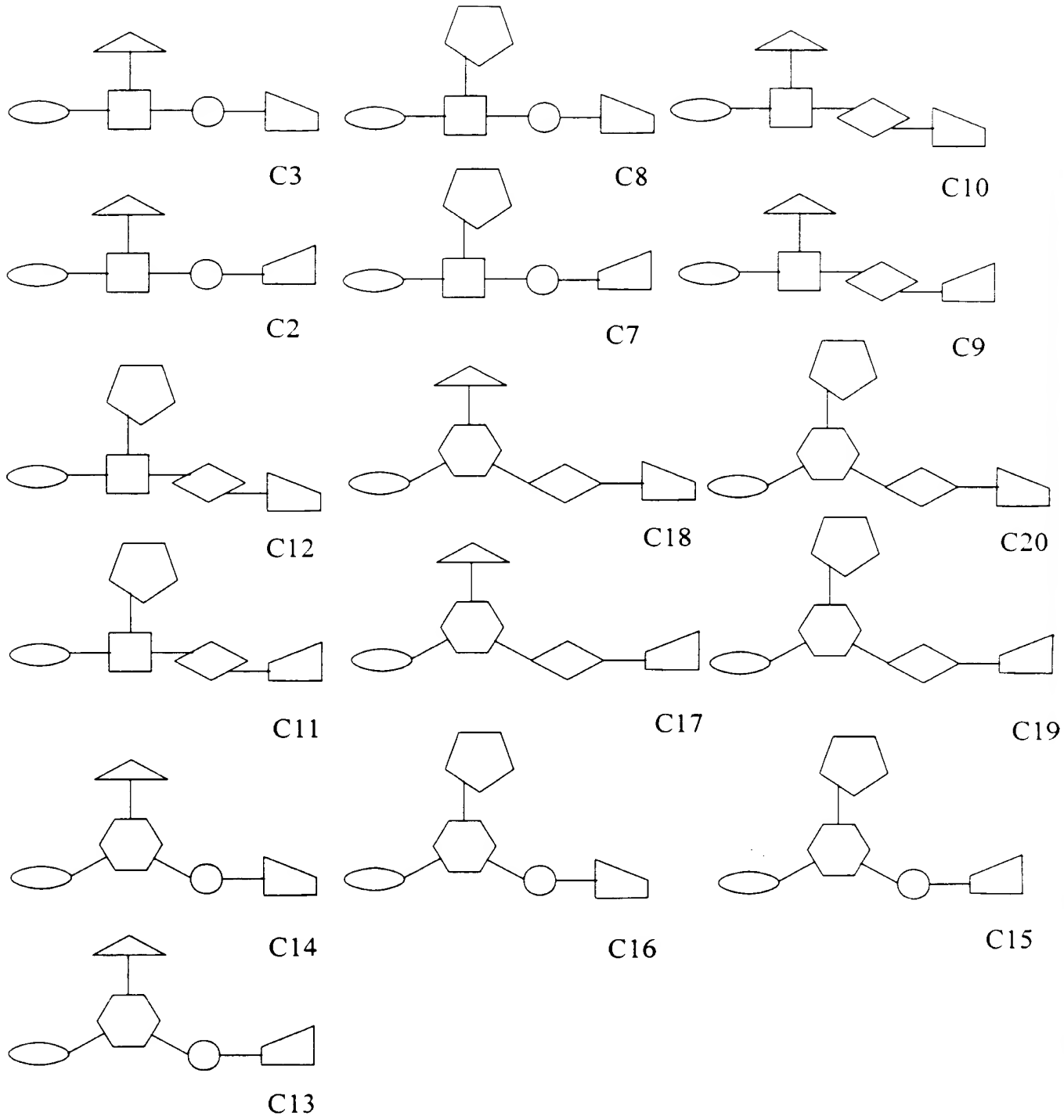


FIGURE 27B

Tracking Table for Compound C1

(a) By Fragments:

n	n+1	n+2
F7	F2	
	F1	
	F5	
		F3

(b) By Transformations:

Synthesis Path 1

n	n+1	n+2
T9	T2	
	T1	
	T6	
		T3

Synthesis Path 2

n	n+1	n+2
T9	T2	
	T1	
	T7	
		T3

Synthesis Path 3

n	n+1	n+2
T9	T2	
	T1	
	T6	
		T4

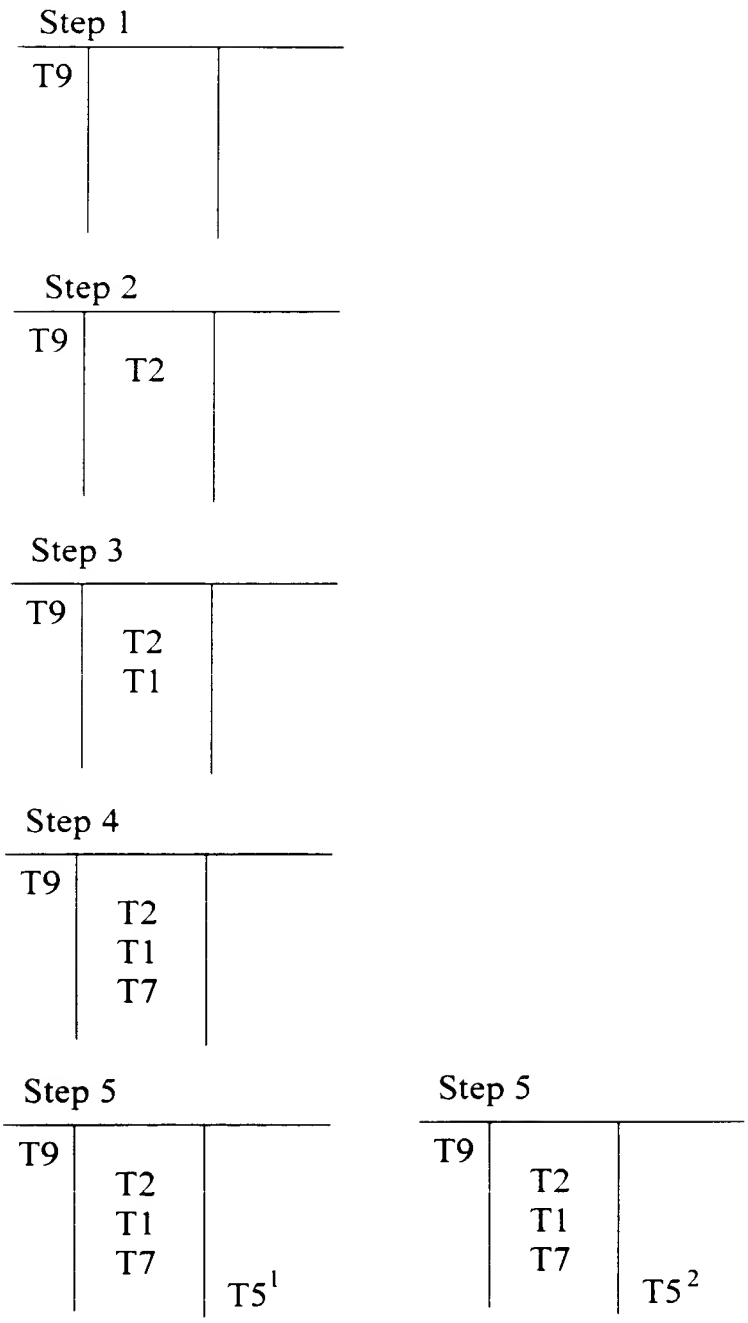
Synthesis Path 4

n	n+1	n+2
T9	T2	
	T1	
	T7	
		T4

FIGURE 28

Tracking Table

Tracking M1



C2 C3

FIGURE 29

Tracking Table

Tracking M2

Step 1

n	n+1	n+2
T9		

Step 1

n	n+1	n+2
T10		

Step 2

n	n+1	n+2
T9	T2	

Step 2

n	n+1	n+2
T10	T2	

Step 3

n	n+1	n+2
T9	T2 T1	

Step 3

n	n+1	n+2
T10	T2 T1	

Step 4

n	n+1	n+2
T9	T2 T1 T7	

Step 4

n	n+1	n+2
T10	T2 T1 T7	

Step 5

n	n+1	n+2
T9	T2 T1 T7	T4

Step 5

n	n+1	n+2
T10	T2 T1 T7	T4

C1

C5

FIGURE 30

Tracking Table

Tracking M3

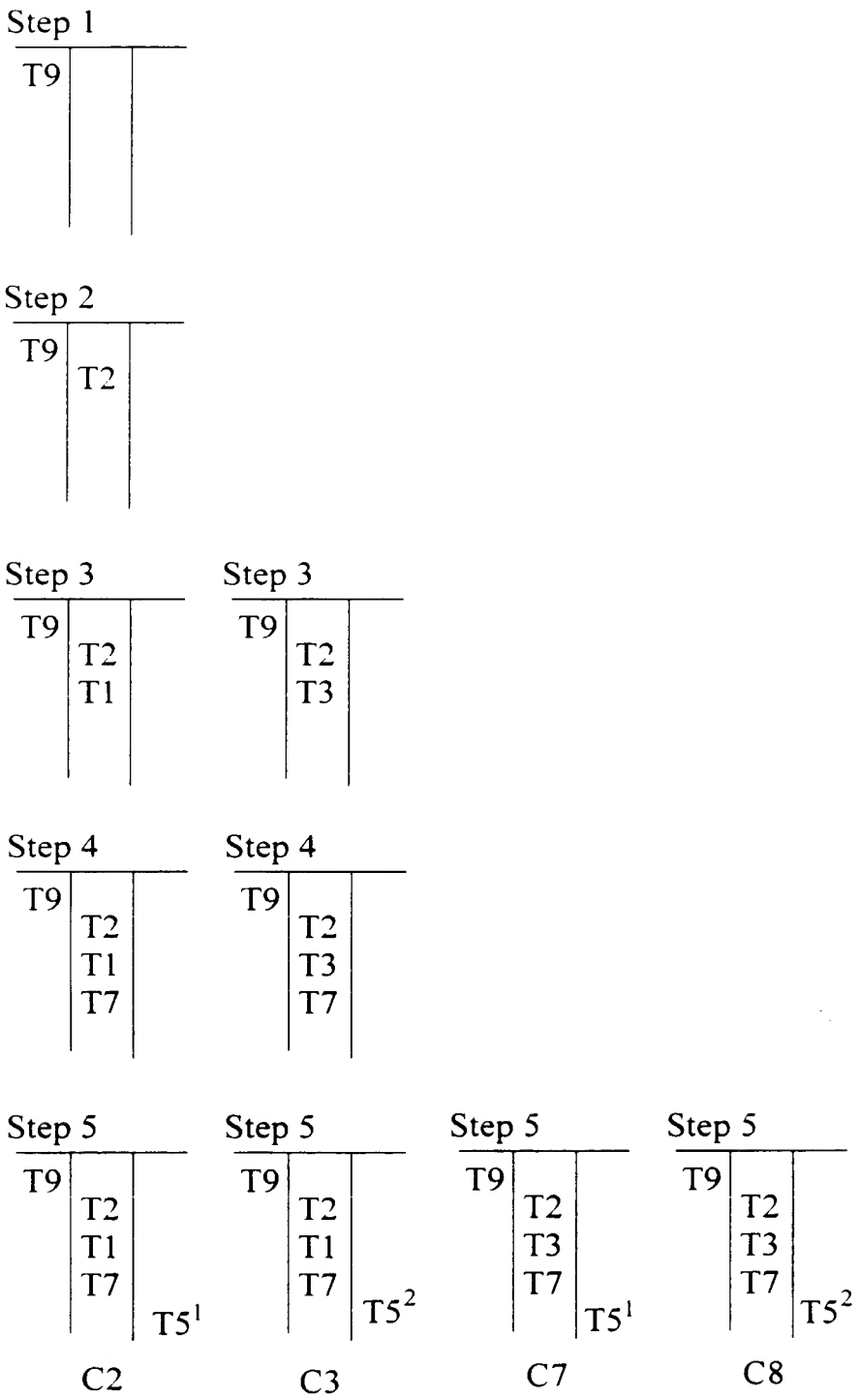


FIGURE 31

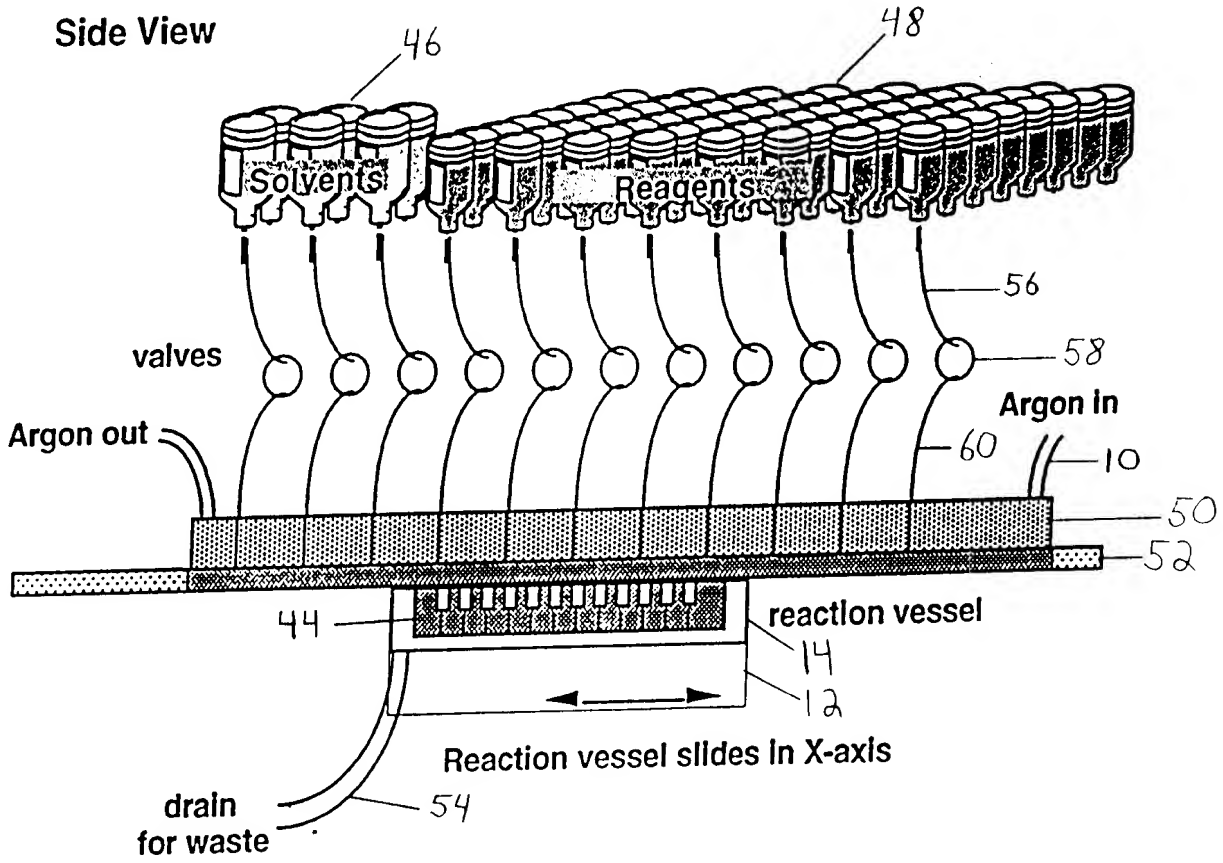

Side View
46
48
Solvents
Reagents
56
valves
58
Argon in
Argon out
60
10
50
52
44
reaction vessel
14
12
Reaction vessel slides in X-axis
drain
for waste
54

FIGURE 32

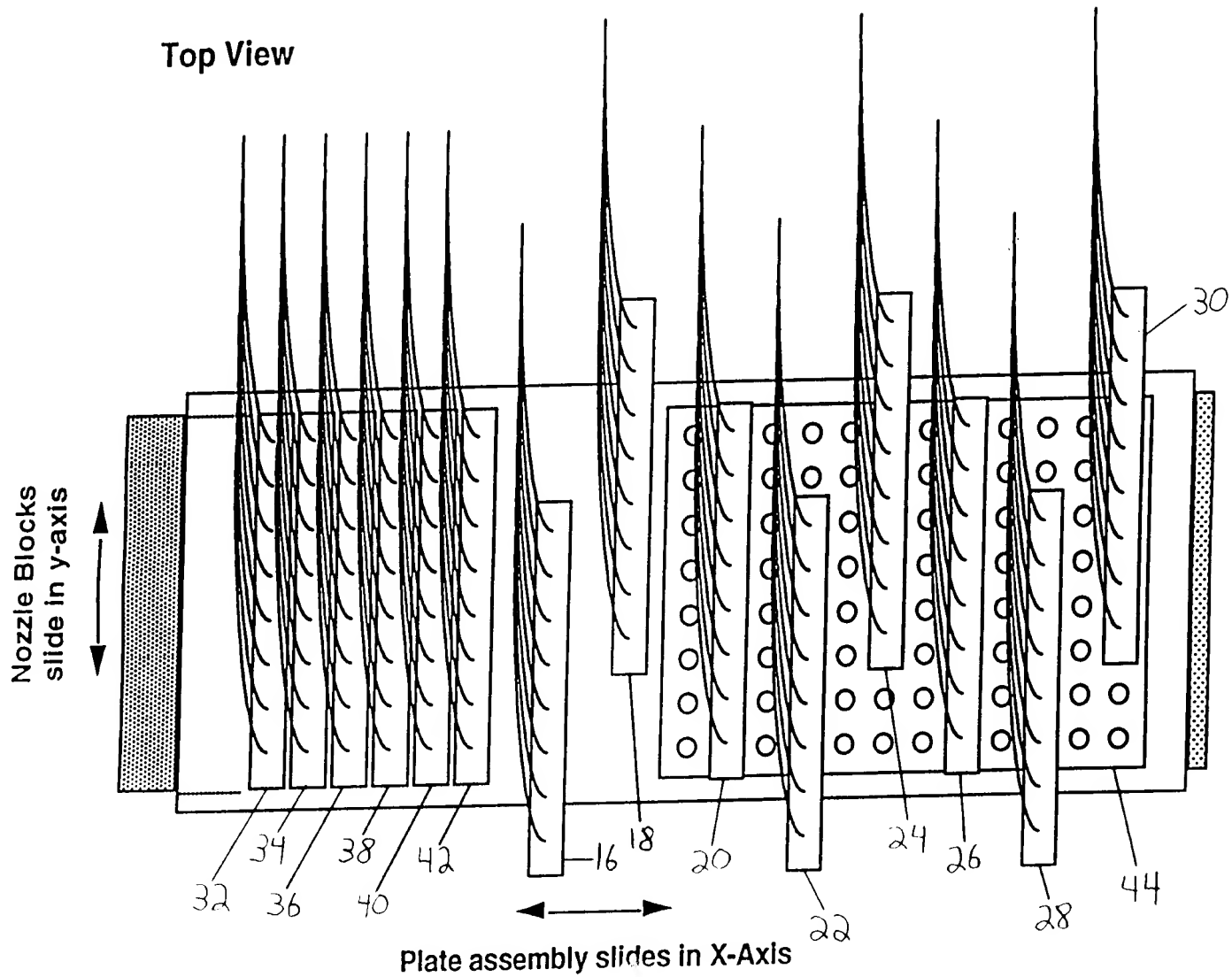
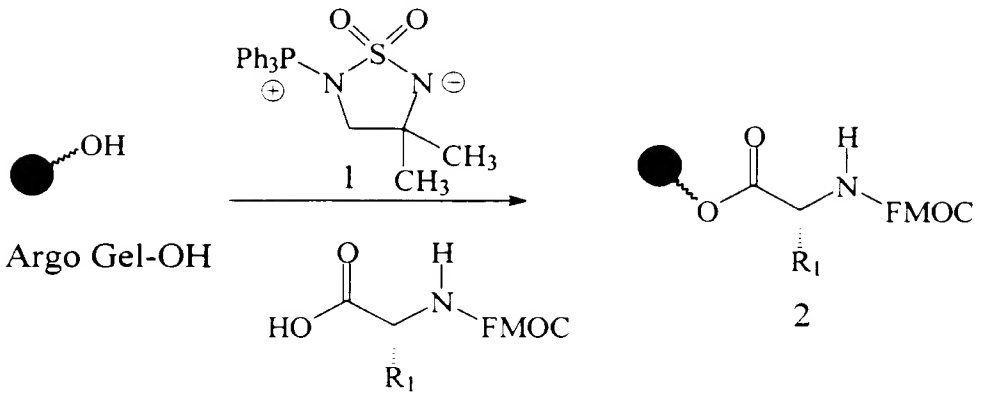
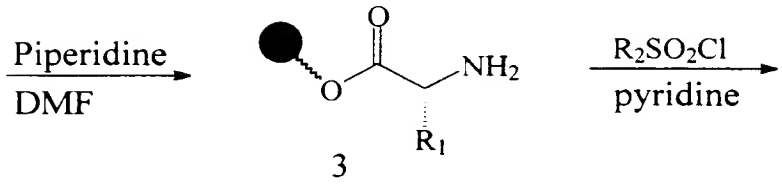

Top View
Nozzle Blocks slide in y-axis
30
32
34
36
38
40
42
16
18
20
22
24
26
28
44
Plate assembly slides in X-Axis

FIGURE 33

Synthesis of hydroxamic acids from alcohol resin





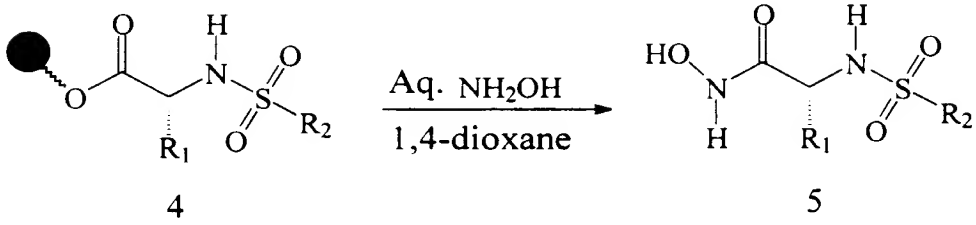
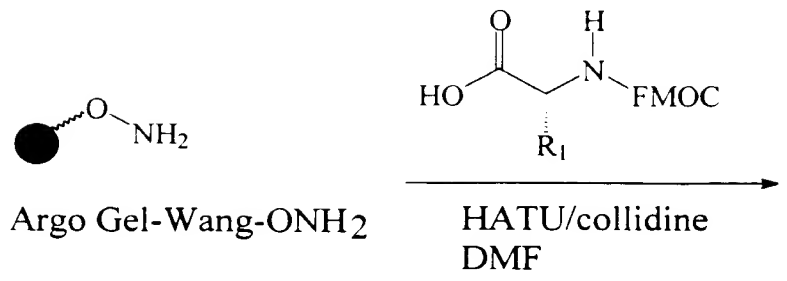


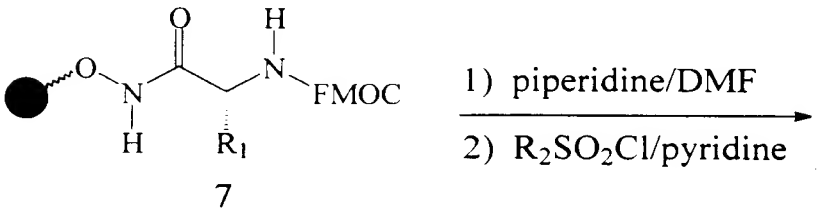
FIGURE 34

Synthesis of hydroxamic acids from hydroxylamine resin



Argo Gel-Wang-ONH2

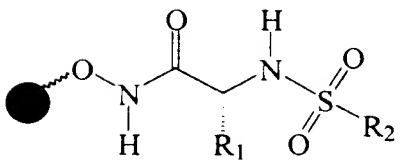
HATU/collidine
DMF



7

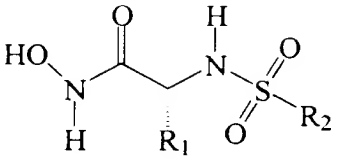
1) piperidine/DMF

2) R_2SO_2Cl/pyridine



8

CF_3CO_2H



5

FIGURE 35

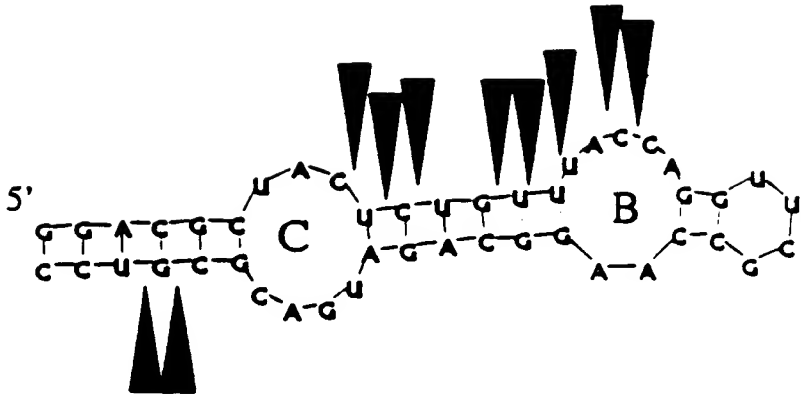


FIGURE 36

Biological Activity and Binding Energy for Structures Docked to TAR with Solvation/Desolvation Energy

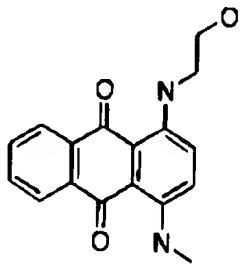
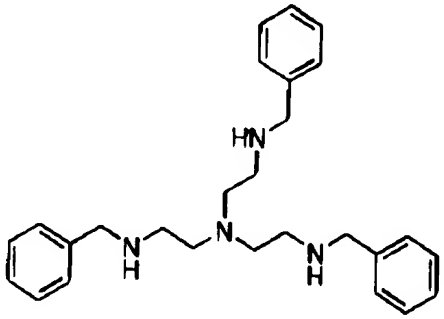
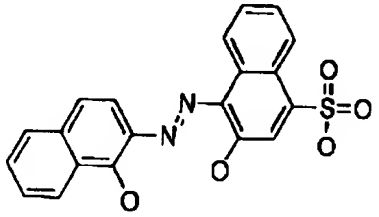
ACD Code	Structure	Calc. ΔG of binding (kcal/mole)	IC_{50} (μM)
00001199		-5.1	<2
00192509		-8.5	<2
00003934		-5.1	<50

FIGURE 37

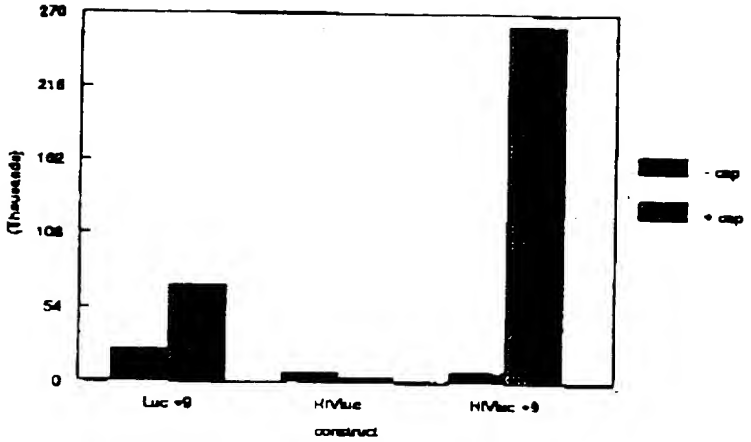


FIGURE 38A

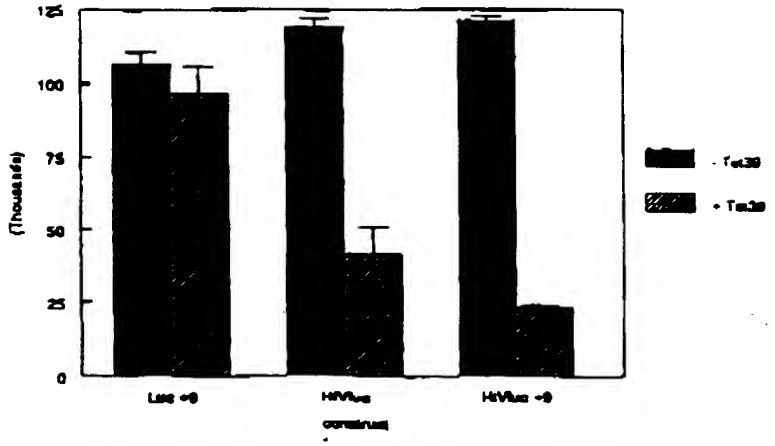


FIGURE 38B

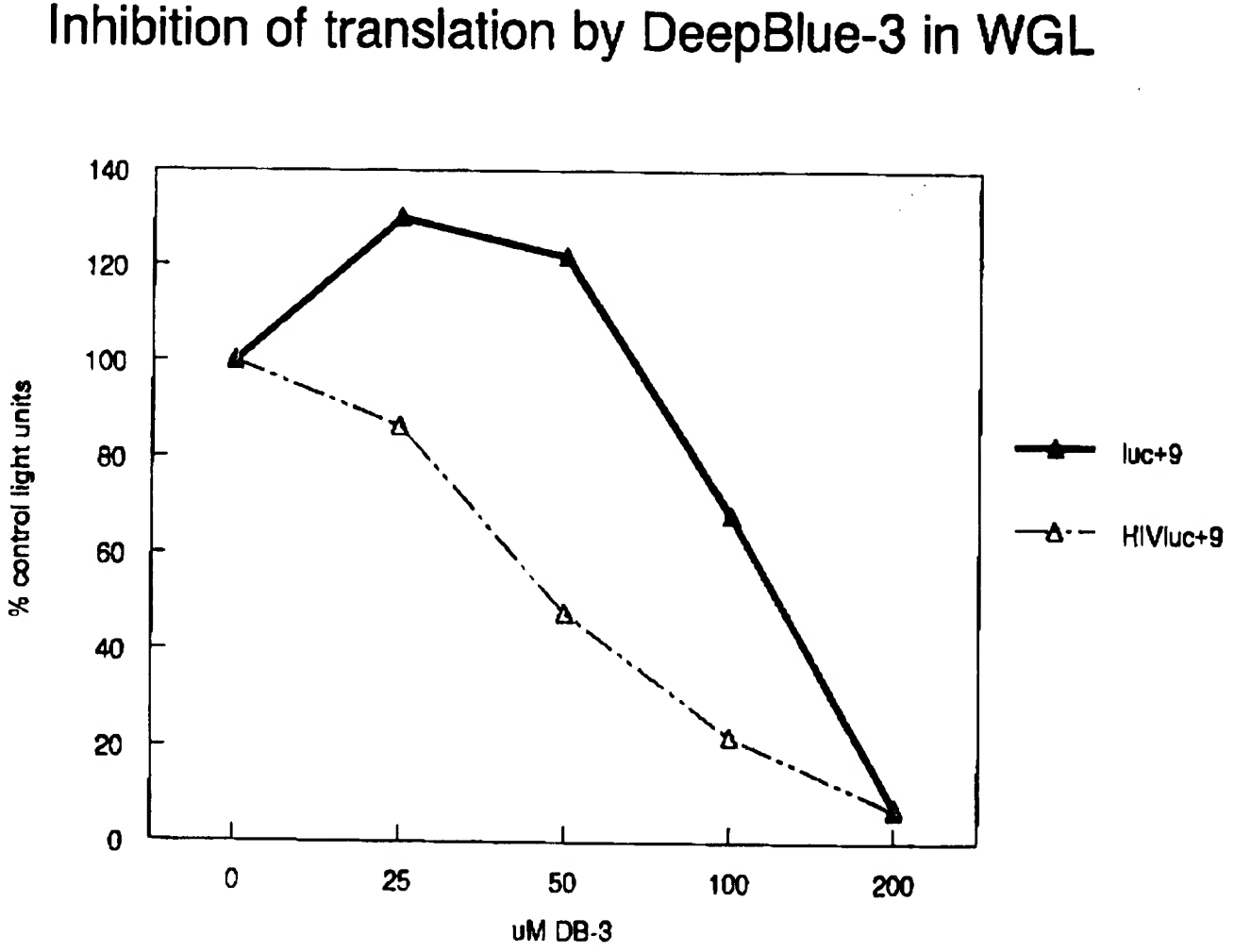
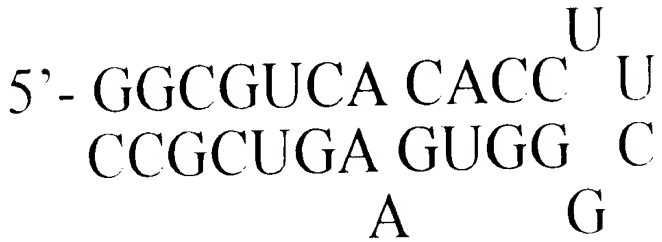
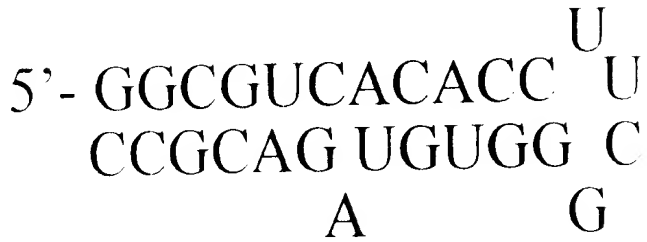

Inhibition of translation by DeepBlue-3 in WGL
% control light units
140
120
100
80
60
40
20
0
0
25
50
100
200
uM DB-3
luc+9
HIVluc+9

FIGURE 39



16S A Site rRNA



Control RNA

FIGURE 40 Sequence and structure of 27mer RNA target

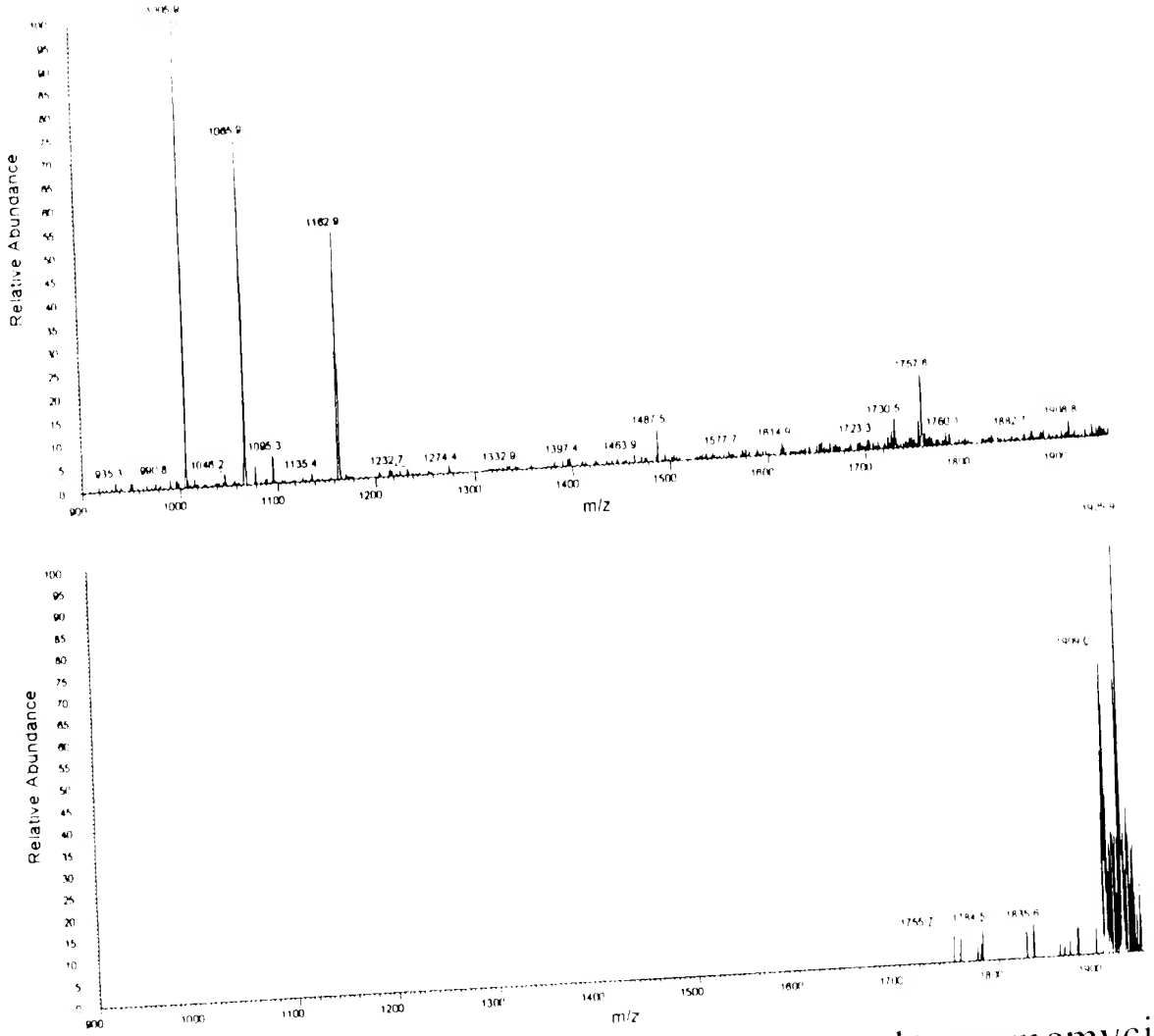


FIGURE 41 MS/MS of control RNA/DNA (upper); control+paromomycin (lower)

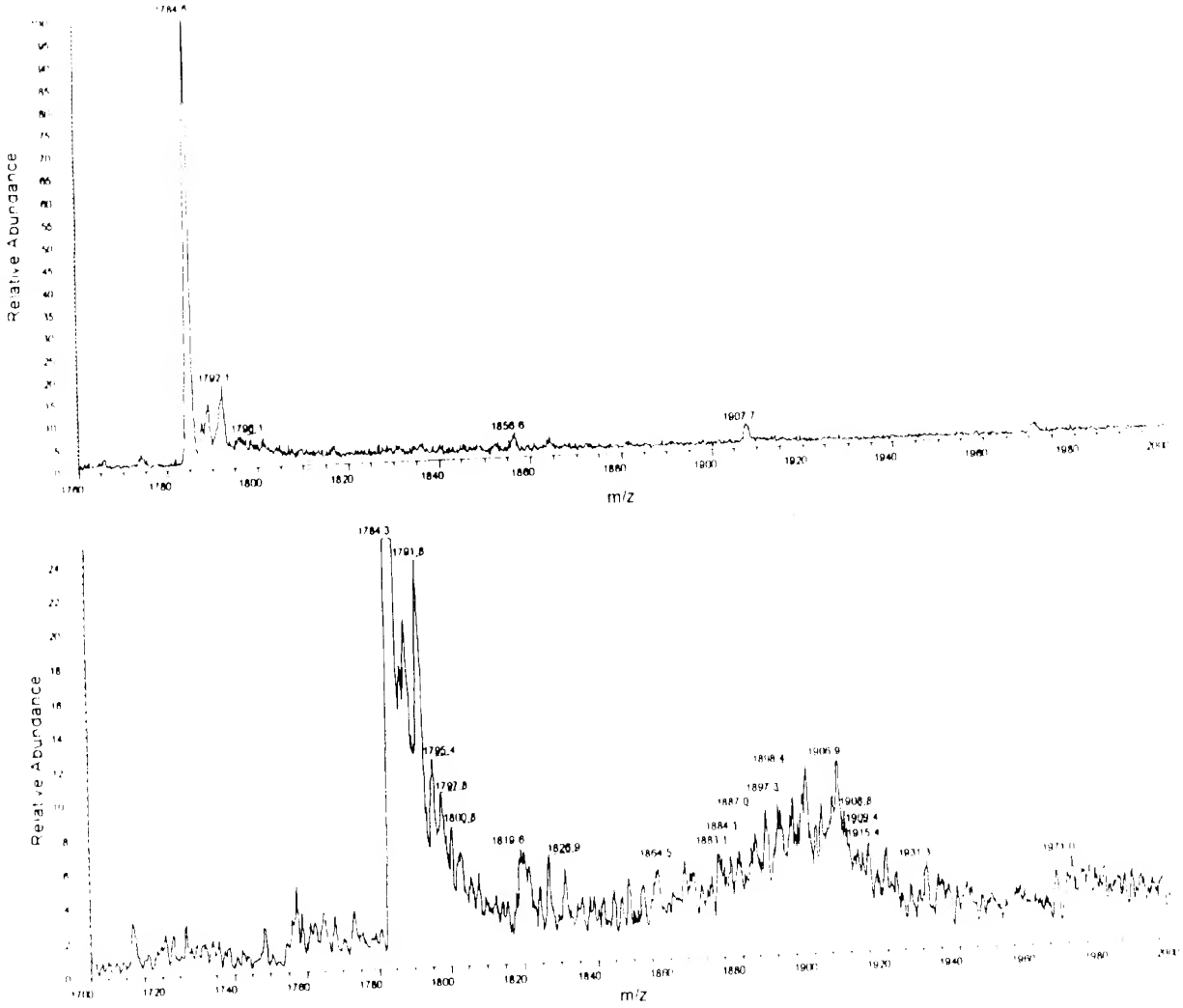


FIGURE 42 RNA/DNA chimera+paramomycin (upper); chimera+library (lower)

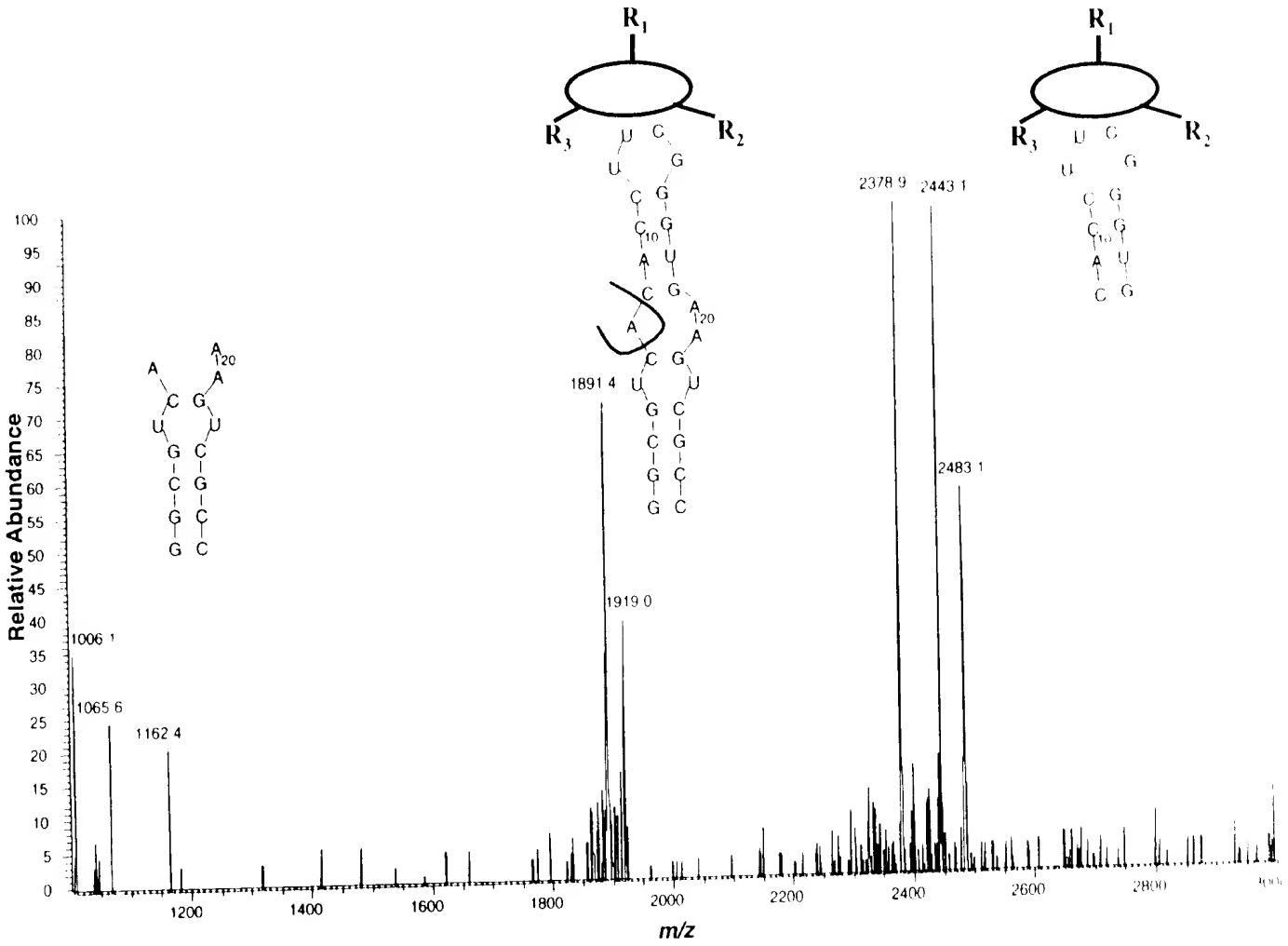


FIGURE 43 MS-MS analysis of member bound to RNA/DNA chimera

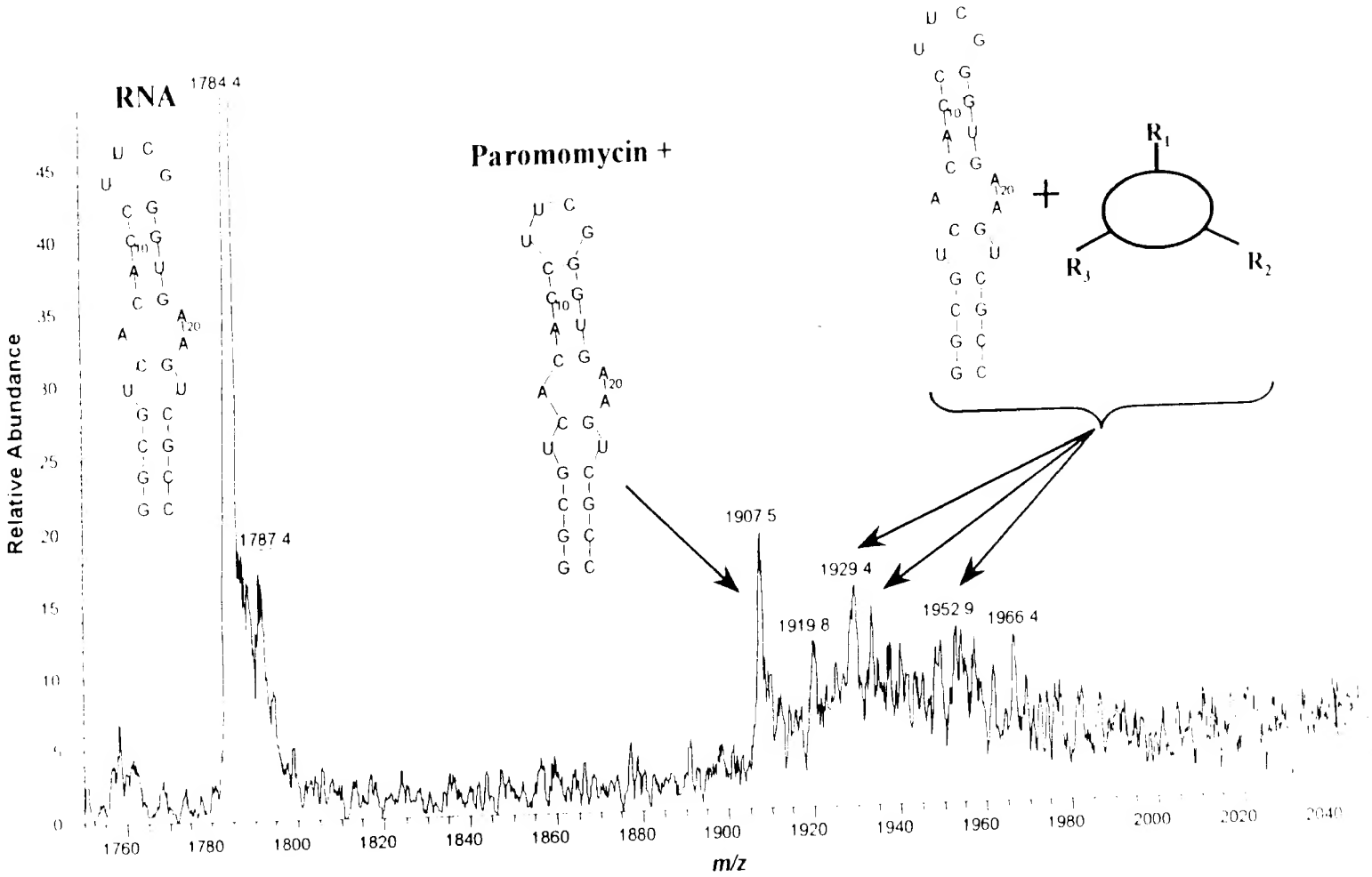


FIGURE 44 ESI-MS of RNA/DNA chimera bound to paromomycin and library

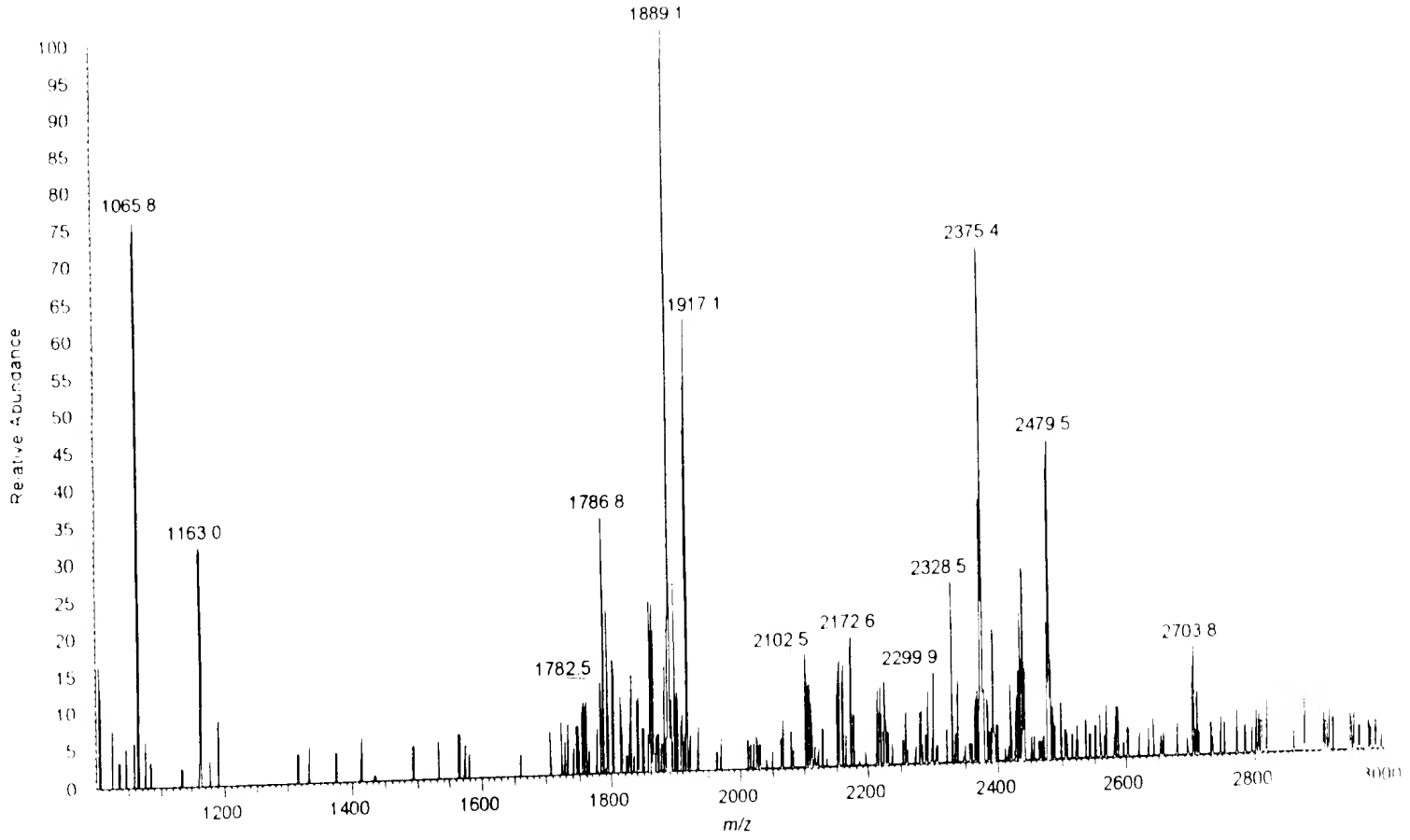


FIGURE 45 MS/MS of RNA/DNA chimera + compound with mass 665.1 not bound at the A-site

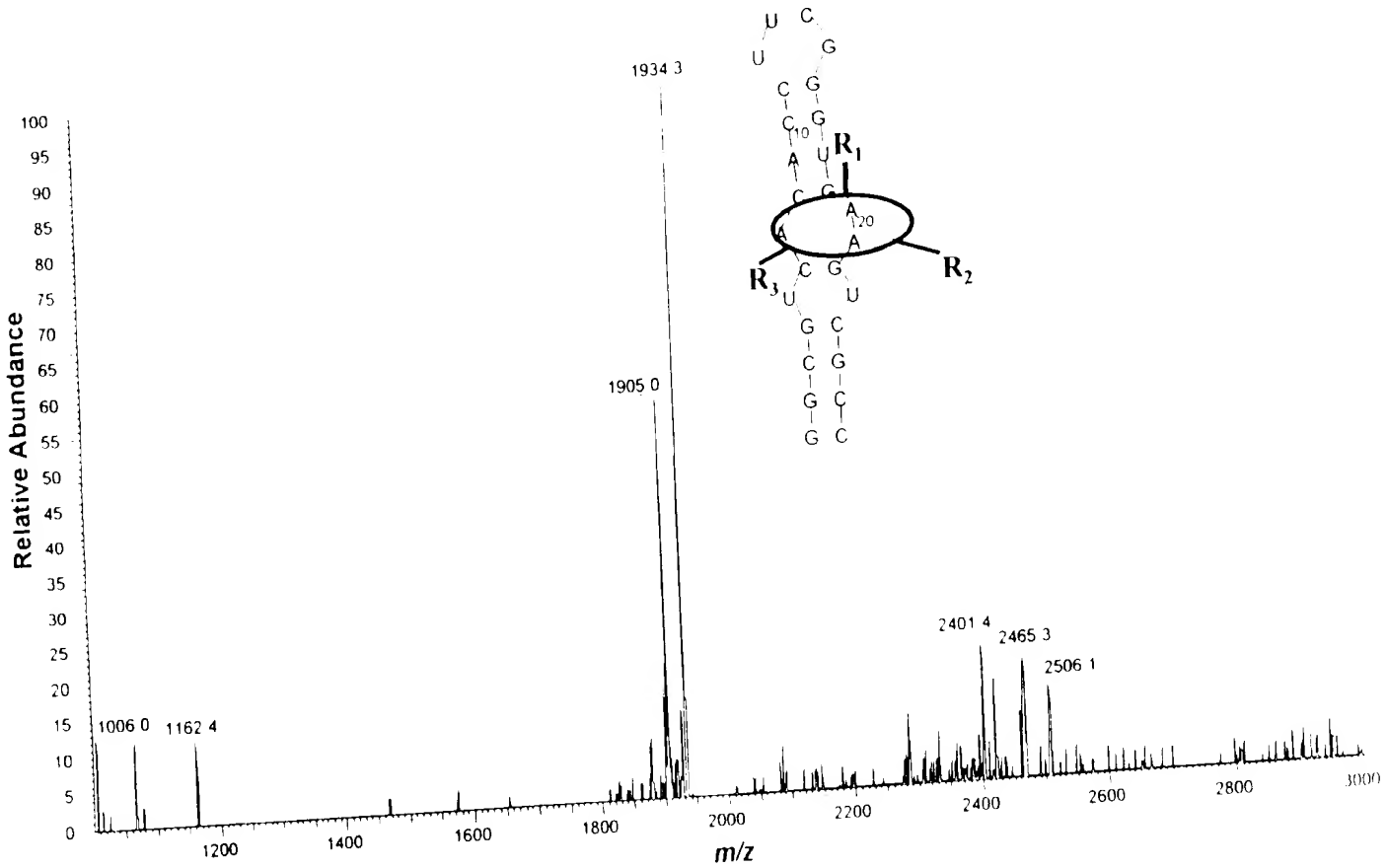


FIGURE 46 MS-MS analysis of member bound to RNA/DNA chimera at the A-Site

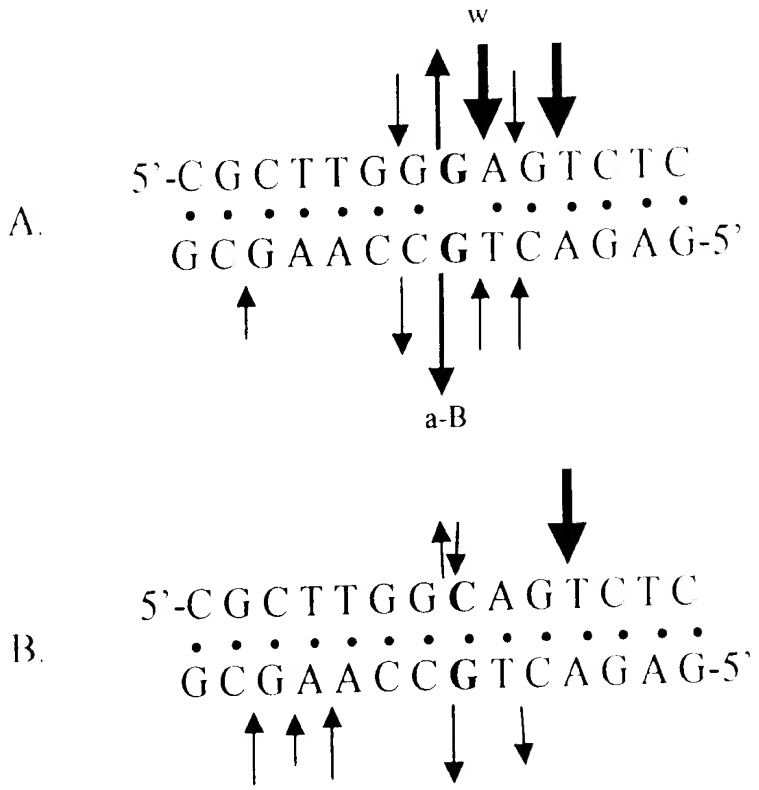


FIGURE 47 MS Fragmentation of DNA:DNA duplexes

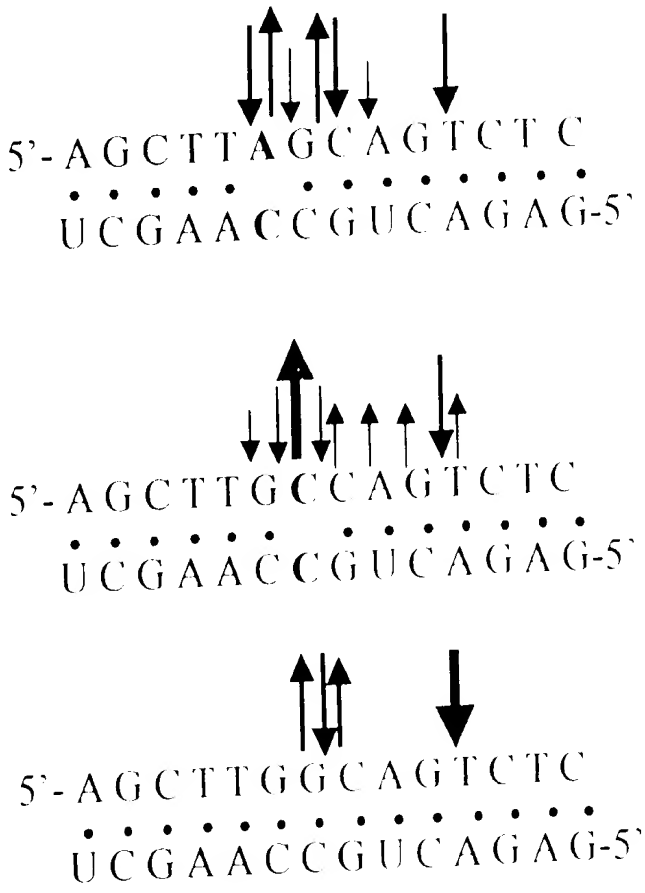
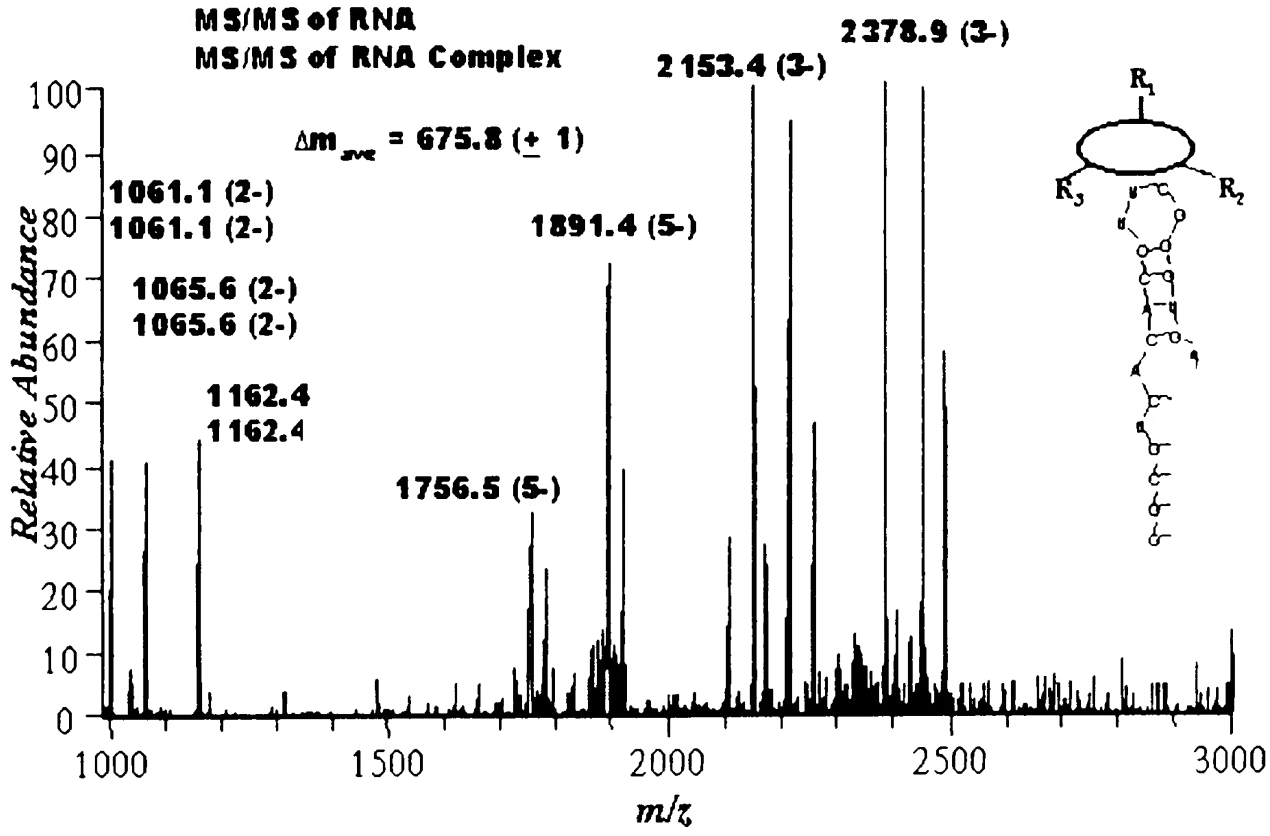


FIGURE 48 MS Fragmentation of DNA:RNA duplexes

MASS Analysis of Binding Location

non-A site binder

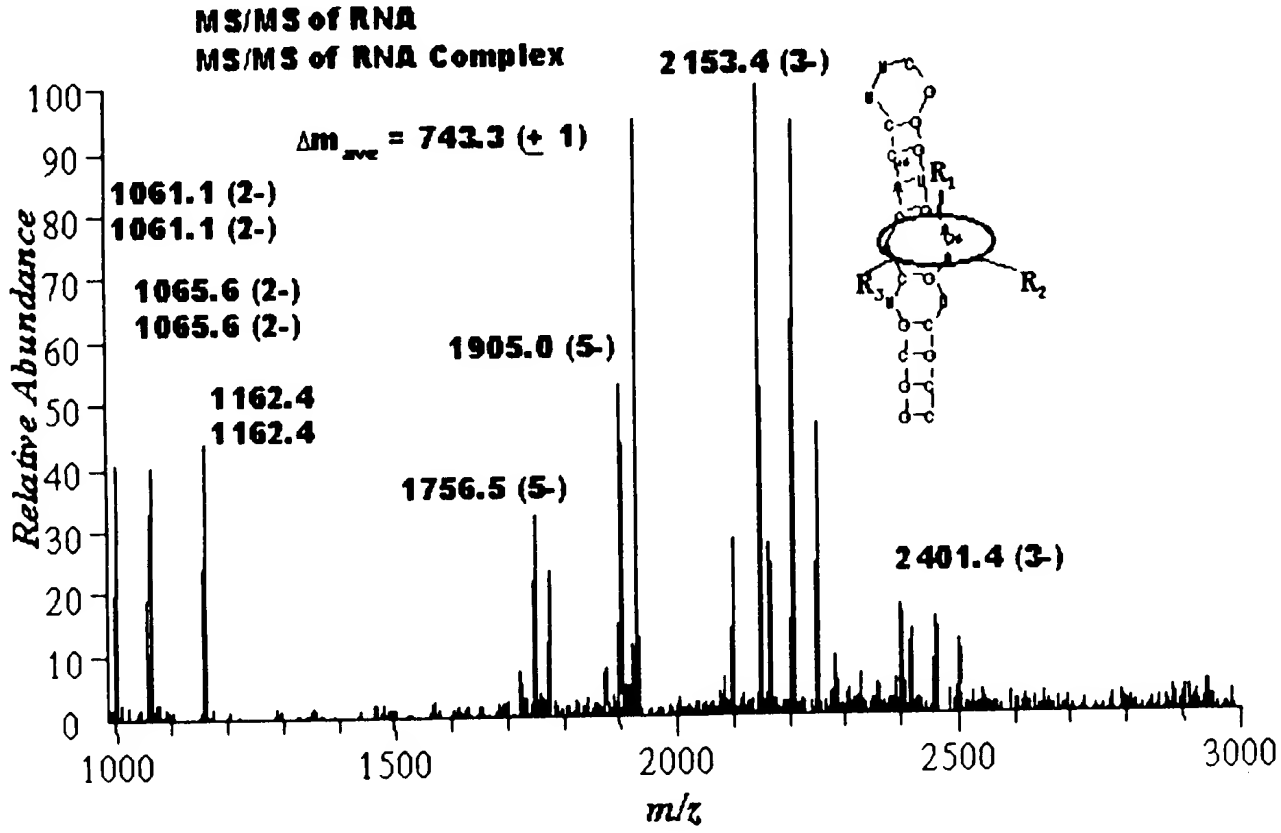
FIGURE 49



MASS Analysis of Binding Location

non-A site binder

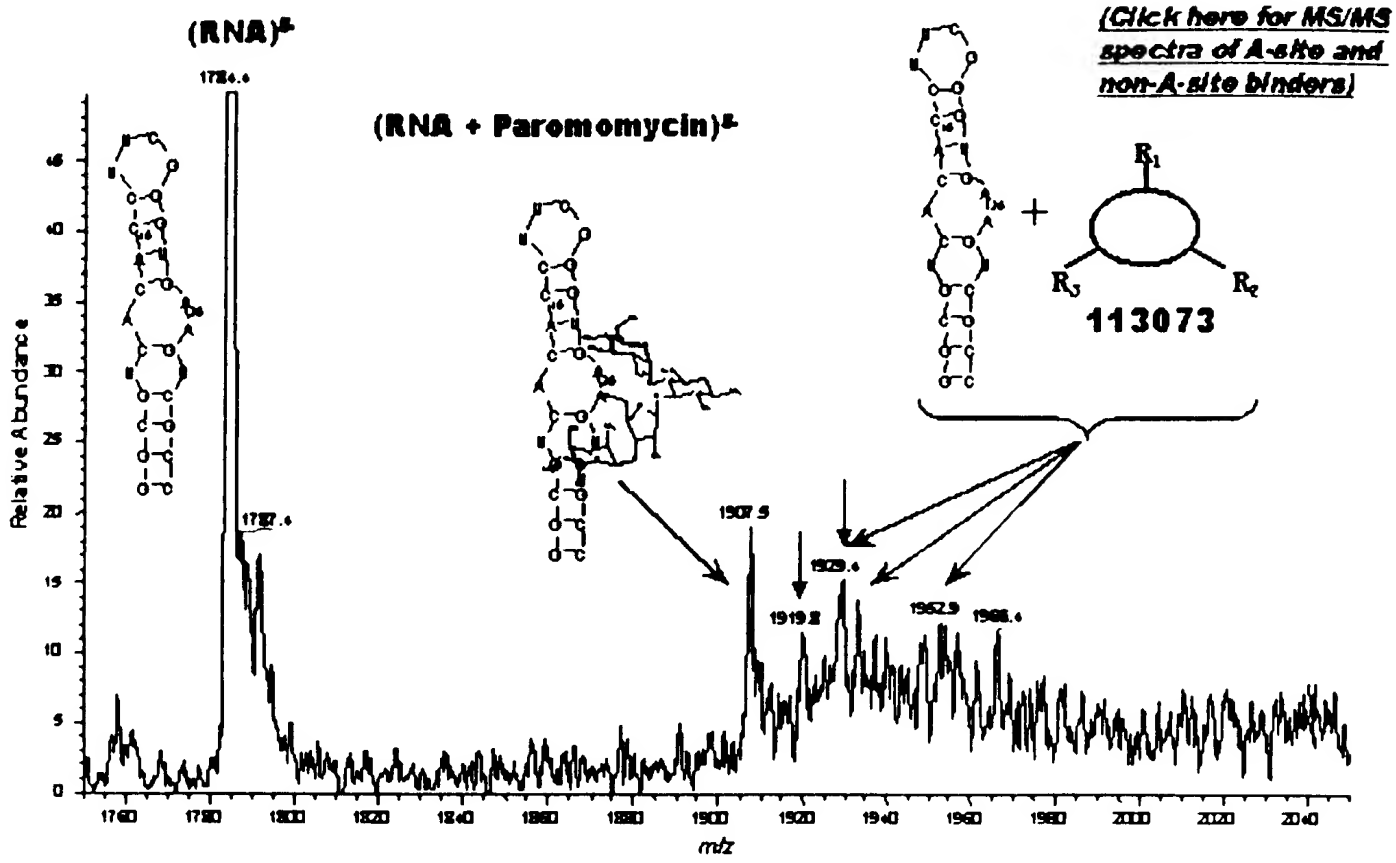
FIGURE 50



MASS analysis of 16S A site RNA plus 216 member library

FIGURE 51

(performed on quadrupole ion trap)



High Precision ESI-FTICR Mass Measurement of 16S A site RNA/Paromomycin Complex

FIGURE 52